Overview of Bayesian Hierarchical Model

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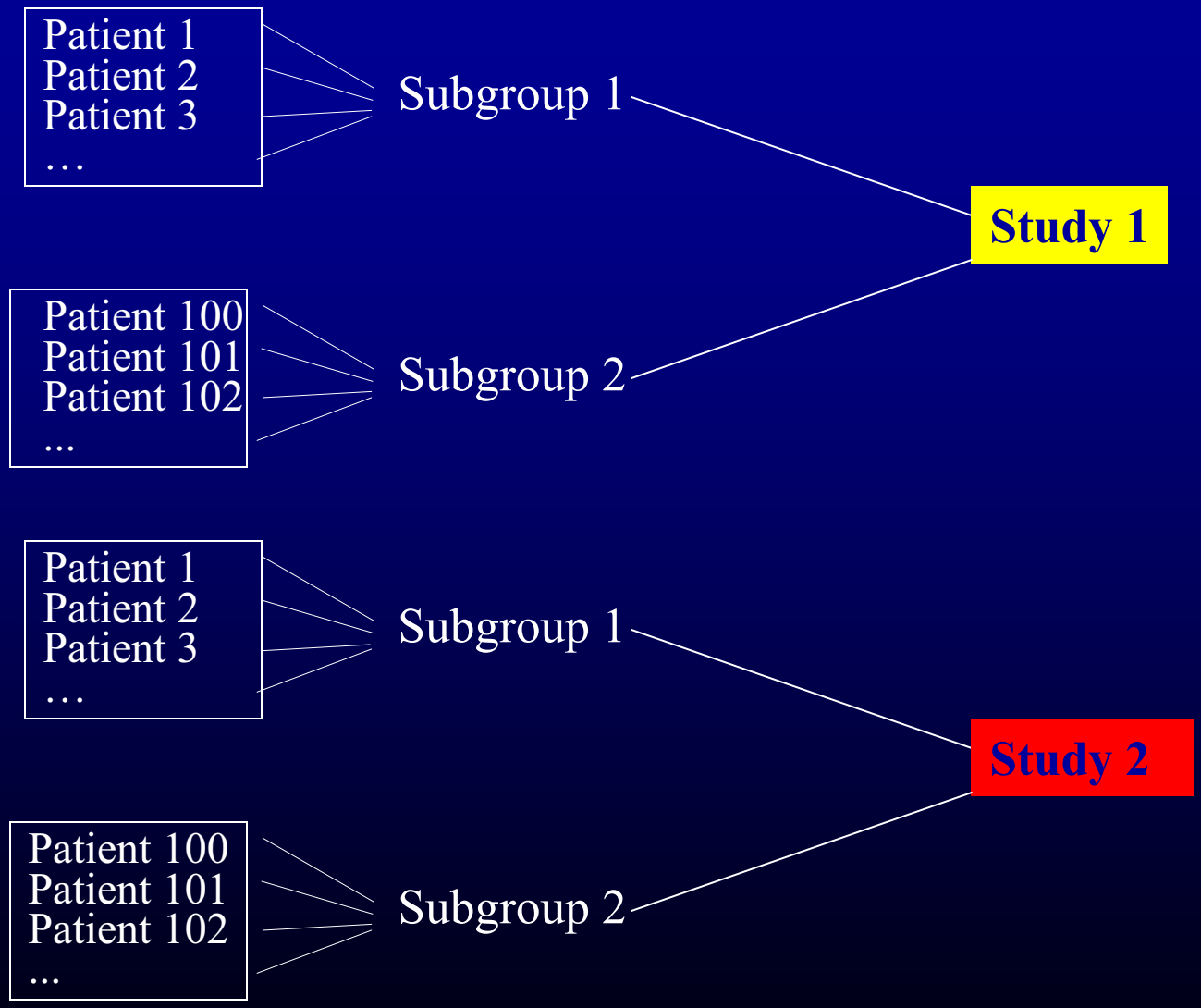
Hierarchical Structure



Hierarchical Models

Flexibly utilize data on related quantities.

Applications:
Estimate device effect in current study by borrowing strength from related studies.

Estimate device effect in a subgroup by borrowing strength from other subgroups.

Hierarchical Models

An Intuitively Appealing Property:

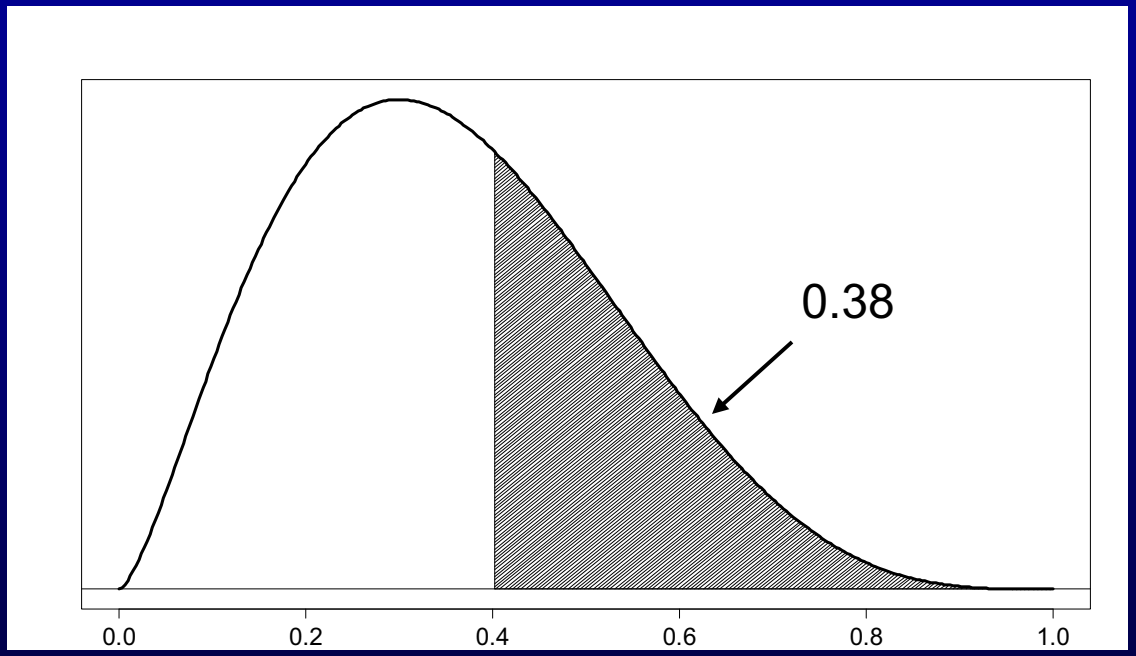
- Borrowing *increases*
  as variability between studies *decreases*

Bayesian Statistics

- Bayesian method is an approach for learning from evidence as it accumulates.
- It uses *Bayes' Theorem* to combine prior information with new data collected in current study, to obtain the posterior distribution on a quantity of interest (e.g., AE rate).
- At the conclusion of the current study, the information about the quantity of interest is summarized by this posterior distribution, and Bayesian inferences are based on it.

Hypothetical Prior Distribution on an Adverse Event Rate

Prior Mean = 0.35

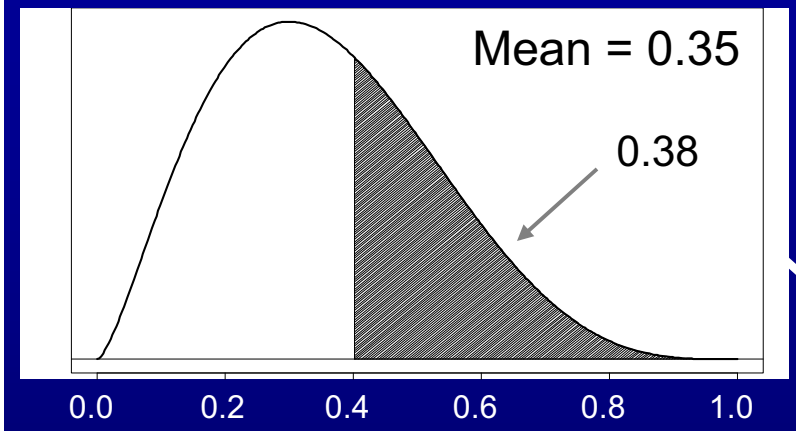


Hypothetical target = 0.40

Prior Probability that AE > 0.40 = 0.38

Learning from Data

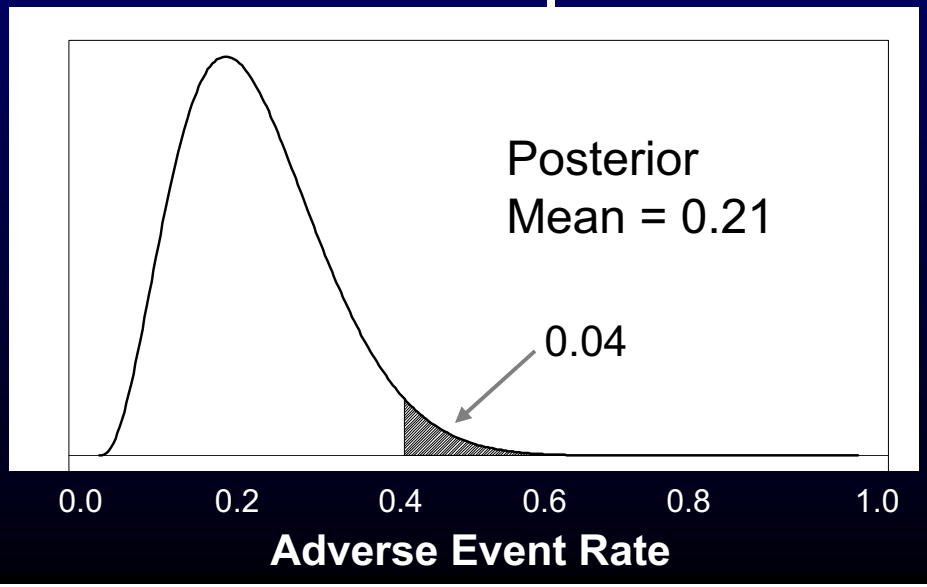
Prior



Study (n=10)

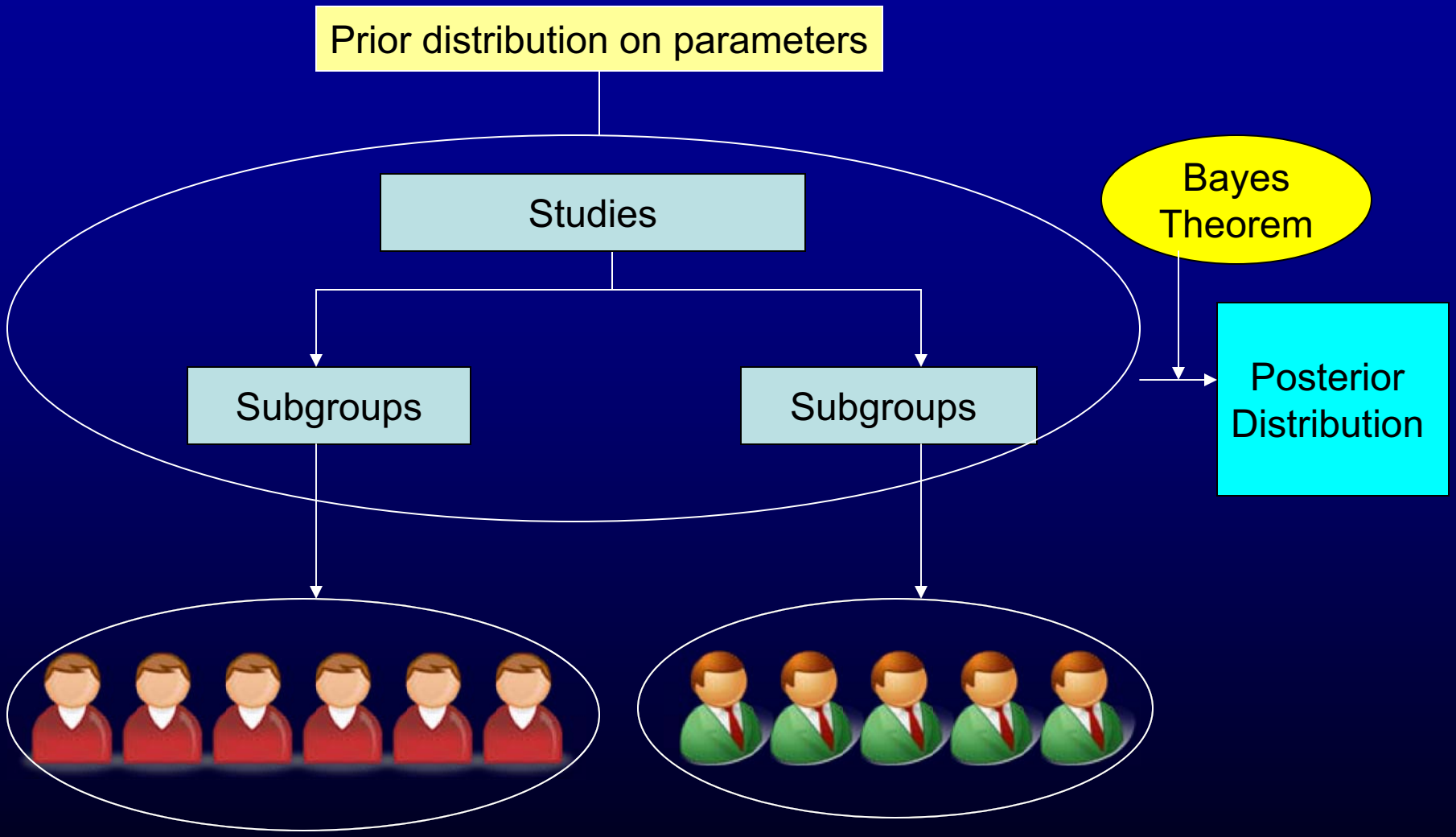
Data: 1 in 10 patients with AEs

Bayes Theorem



Posterior:
the updated prior distribution after seeing the current data

Hierarchical Model in Bayesian Framework



TherOx® Downstream® Aqueous Oxygen (AO) System

FDA review of P080005

Catherine P. Wentz, M.S.
Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

Circulatory System Devices Panel Meeting
March 18, 2009

FDA Team Presenters

Catherine Wentz, MS

Introductory and pre-clinical

Vandana Mukhi, PhD

Statistical

Julie Swain, MD

Clinical

Shaokui Wei, MD

Epidemiology – post-approval study

Outline

- Regulatory History
- Proposed Indications for use
- Device Description
- Pre-clinical
- Study Overview

Regulatory History

Regulatory History

- **1999**
  - **AMIHOT I feasibility (29 pts, 3 centers)**
- **2002 - 2004**
  - **AMIHOT I Pivotal (289 pts, 23 centers)**
- **2005 – 2007**
  - **AMIHOT II Pivotal (317 pts, 22 centers)**

Indications for Use

Proposed Indications for Use

The AO System is …indicated for the …. delivery of SSO2 Therapy to … ischemic regions of the heart…. immediately following [PCI] …performed within 6 hours … of anterior acute myocardial infarction (AMI) symptoms

[FDA] Proposed Indications for Use

The device is …indicated for the …. delivery of SSO2 Therapy to … ischemic regions of the heart…. immediately following *successful* [PCI] …performed within 6 hours … of anterior acute myocardial infarction (AMI) symptoms

Device Description

Device Description

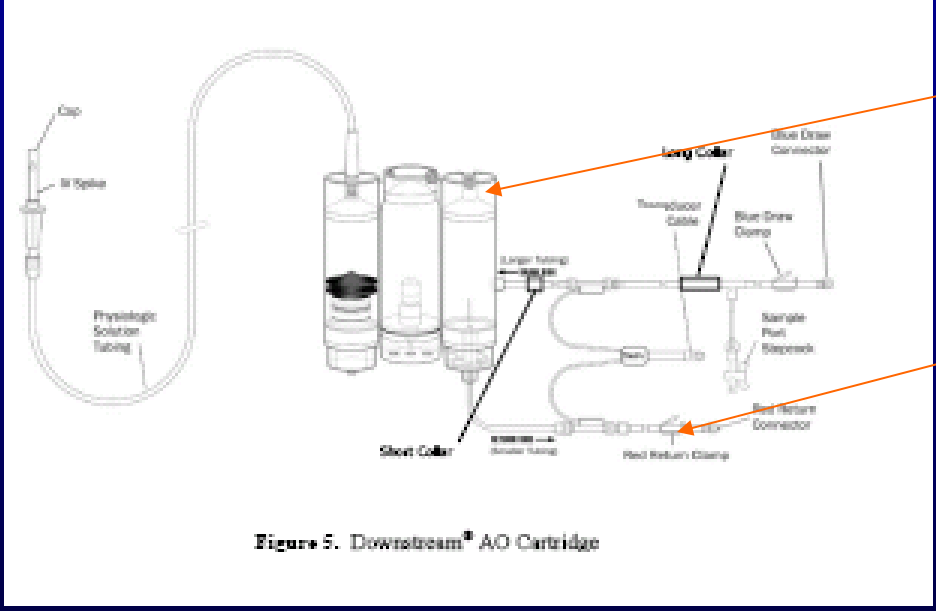


Figure 5. Downstream® AO Cartridge

- Patient's blood mixed with hyper-oxygenated saline solution made in the chamber
- 72ml blood:3ml (75ml/min) AO solution delivered to infarct via infusion catheter (positioned within implanted stent)
- 90 minutes
- Following successful PCI

MI-Cath Infusion Catheter

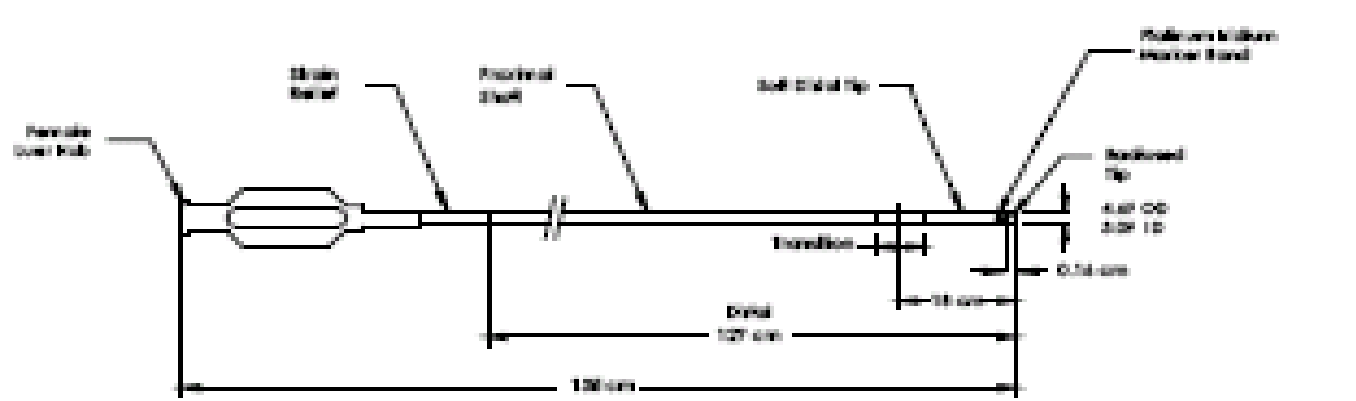


Figure 6. MI-Cath Infusion Cather

CHARACTERISTIC	MI-Cath	TRACKER-38
Outer Diameter	4.6 Fr (1.38mm) overall	5.3Fr (1.6mm) 5.0Fr (1.5mm) at tip
Inner Diameter	1.06mm overall 0.85mm minimum at marker band	1.06mm overall 0.92mm at marker band
Usable Length	127 cm	115 cm
Materials	High Density polyethylene (HDPE) shaft and luer, LDPE plasticized tip	Polypropylene/LDPE shaft, thermoplastic luer, LDPE plasticized tip

Preclinical Testing

FDA Pre-clinical Review Team

- **Catherine Wentz**, B.S., M.S.– Team Leader
  - *Engineering*
- **Bill Riemenschneider**, B.S., M.S.
  - *In vivo/animal review*
- **Contress Braxton**, PhD
  - *Bio-research monitoring*
- **Mary Ann Fitzgerald,** B.S.
  - *Manufacturing*
- **Lisa Kennell**, B.S.
  - *Microbiologist/Biocompatibility*
- **Sharon Lappalainen,** B.A., MT (ASCP)
  - *Microbiologist/Sterilization/Packaging*
- **Jonathan Helfgott**, B.S., M.S.
  - *Software*

Pre-clinical Review – *In Vitro*

***In Vitro* Bench Studies**
Software
Biocompatibility
Sterilization/Packaging
Manufacturing
Bio-research Monitoring

Methods/Results - Verified/Validated
No further concerns in these areas

Pre-clinical Review *In vivo*

- **Limitations**
  - **small number of animals**
  - **mostly acute studies**
  - **healthy, infarcted juvenile swine vs. older, diseased human arteries**

- **Results**
  - **smaller infarct size,**
  - **necrosis studies on at-risk tissue for O2 toxicity effect**
  - **no evidence of embolic events**

- **SSO_2 employed in > 350 patients - clinical safety data to address the remaining questions unable to be obtained through the *in vivo* model**

Study Overview

Study Overview

- **AMIHOT I (2002 – 2004)**
- **AMIHOT II (2005 – 2007)**

AMIHOT I

- **RCS (1:1), 289 patients, 23 centers**
- **Patient Population**
  - **AMI (symptom onset < 24 hours)**
  - **Anterior or Non-anterior Infarct**
  - **Successful angioplasty/stenting**
- **Endpoints**
  - **Safety**
    - **MACE - death, reinfarction, TVR, stroke within 30 days**
  - **Effectiveness**
    - **infarct size at 14 days post PTCA/Stent placement**
    - **WMSI at three months**
    - **ST-segment recovery during the first three hours**
- **Failed study** – analysis of results used to generate hypotheses for AMIHOT II

AMIHOT II

- **RCS (2.8:1), Bayesian methods, 317 patients, 22 centers**
- **Patient Population** (subset of AMIHOT I)
  - **AMI (symptom onset < 6 hours)**
  - **Anterior Infarct Only**
  - **Successful angioplasty/stenting**

- **Endpoints**
  - **Safety**
    - **MACE - death, reinfarction, TVR, stroke within 30 days**
  - **Effectiveness**
    - **PRIMARY - infarct size at 14 days post PCI**
    - **SECONDARY - ST-segment recovery during the first three hours**

Following FDA Presenters

- **Vandana Mukhi, PhD – statistical presentation AMIHOT I and II study results**

- **Julie Swain, MD**
- **Shaokui Wei, MD**

TherOx AO System

FDA Statistical Perspective

Vandana Mukhi, Ph.D.
Division of Biostatistics
Office of Surveillance and Biometrics
Food and Drug Administration

March 18, 2009

Outline

- Earlier Study: AMIHOT I
  - Study Design
  - Primary Endpoint Analyses
- Current Study: AMIHOT II (Bayesian)
  - Study Design
  - Primary Endpoint Analyses
  - Additional Analyses
- Summary

AMIHOT I

- Treatment Group: AO therapy after PCI/Stenting
- Control Group: PCI/Stenting alone
- Patient Population
  - AMI (symptom onset < 24 hours)
  - Anterior or Non-anterior Infarct
- Study Enrollment
  - 1:1 Randomization
  - 289 patients (135 AO, 134 Control; 20 run-ins) @ 23 centers

AMIHOT I Primary Endpoints

- Safety (non-inferiority)
  - Composite MACE rate - Death, Reinfarction, Revascularization and Stroke within 30 days.
- Effectiveness (superiority)
  - Infarct Size at 14 days post PCI/Stent placement
  - WMSI at three months
  - ST-segment recovery 0-3 hours

AMIHOT I – Safety Endpoint

- Study met the primary safety endpoint, demonstrating non-inferiority with a margin of 8%.
- Exact test one-sided p-value = 0.022

	Events				Composite MACE	
Group	**Death**	**Reinfarction**	**TVR**	**Stroke**	**# Patients (%)**	**95% C I**
Control (n = 135)	2	3	3	2	7 **(5.2%)**	**(2.1% , 10.4%)**
AO Therapy (n = 134)	4	3	3	1	9 **(6.7%)**	**(3.1% , 12.4%)**

AMIHOT I – Effectiveness Endpoint

- Study failed because none of the three co-primary effectiveness endpoints was met.

Infarct Size (%LV as measured by Tc-99m SPECT)*			
ITT Analysis	**Control (n=122)**	**AO Therapy (n=121)**	**Difference (Trt – Ctrl)**
Mean ± SD	17.4 ± 16.4	16.9 ± 17.5	**-0.5**
Median	13.0	11.0	**-2.0**

*Wilcoxon rank-sum test one-sided p-value = 0.29

RWMSI #			
ITT Analysis	**Control (n=119)**	**AO Therapy (n=115)**	**Difference (Trt – Ctrl)**
Mean ± SD (n)	-0.57 ± 0.48	-0.62 ± 0.53	**-0.05**

#T-test one-sided p-value = 0.24

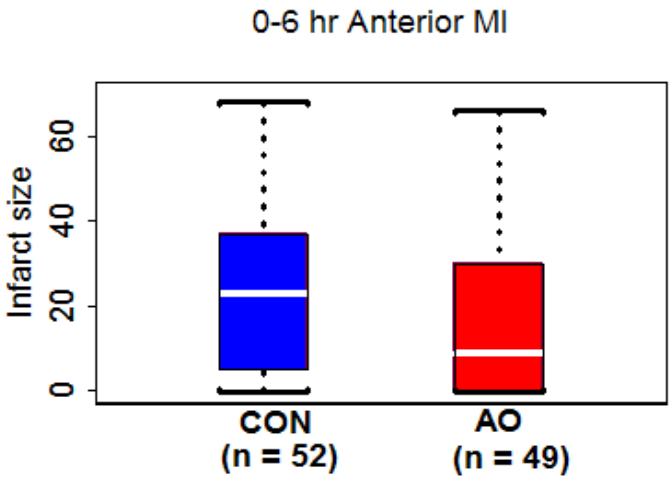
ST-Deviation Time Trend Curve Area Data 0-3 hours post-PCI			
ITT Analysis	**Control (n=117)**	**AO Therapy (n=120)**	**p-value****
Median	0	0	**0.5**

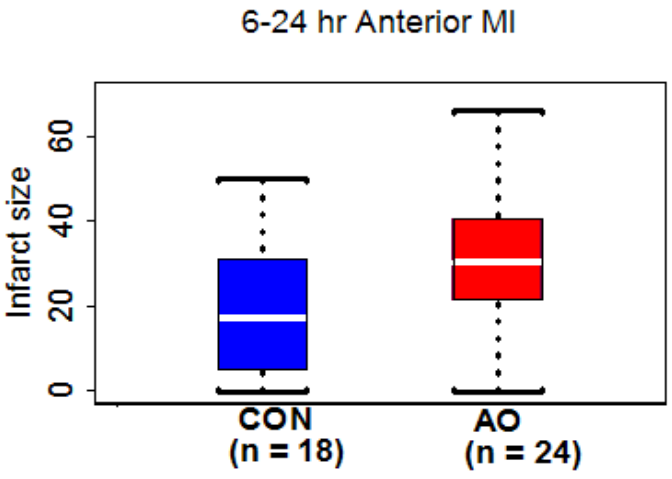
**Wilcoxon rank-sum test one-sided p-value

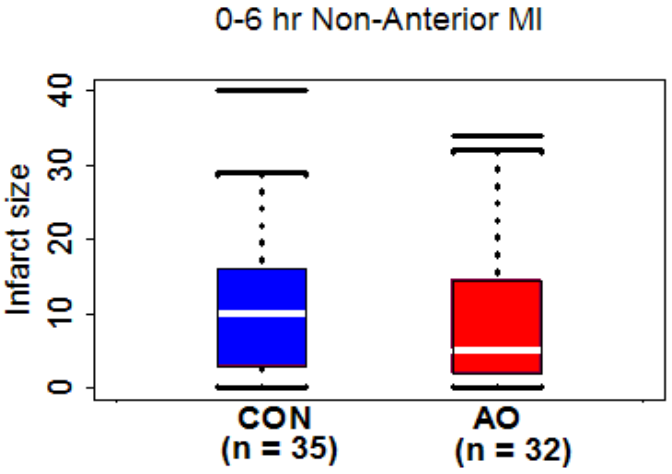
AMIHOT I
Post-hoc Subgroup Analysis

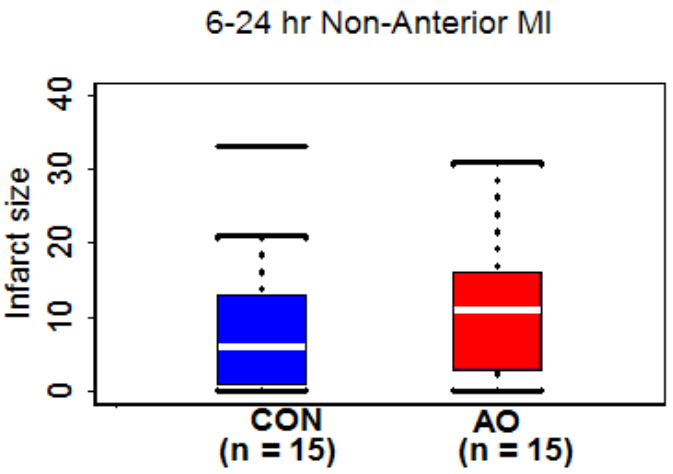
- Pre-specified subgroups include:
  - Time to Reperfusion
    (0-2 hours, 2-6 hours, > 6 hours)
  - Infarct Location
    (Anterior MI vs. Non-Anterior MI)

AMIHOT I - Infarct Size Subgroup Analysis









AMIHOT I
Post-hoc Subgroup Analysis

- Anterior MI patients with ≤ 6 hours PCI

Infarct Size (%LV as measured by Tc-99m SPECT)*			
ITT Analysis	**Control (n=52)**	**AO Therapy (n=49)**	**Difference (Trt – Ctrl)**
Mean ± SD	23.0 ± 18.9	17.3 ± 19.7	**-5.7**
Median	23.0	9.0	**-14.0**

*Wilcoxon rank-sum test one-sided p-value = 0.04

RWMSI#			
ITT Analysis	**Control (n=49)**	**AO Therapy (n=49)**	**Difference (Trt – Ctrl)**
Mean ± SD (n)	-0.54 ± 0.49	-0.75 ± 0.57	**-0.21**

#T-test one-sided p-value = 0.03

ST-Deviation Time Trend Curve Area Data 0-3 hours post-PCI			
ITT Analysis	**Control (n=46)**	**AO Therapy (n=46)**	**p-value****
Median	311	0	**0.01**

**Wilcoxon rank-sum test one-sided p-value

How to Move Forward?

1. Pool AMIHOT II with only AMIHOT I subgroup (Anterior MI ≤ 6 hours)
2. Allow AMIHOT II to borrow from only AMIHOT I subgroup (Anterior MI ≤ 6 hours)
3. Allow AMIHOT II to borrow from all of AMIHOT I
4. AMIHOT II alone

AMIHOT II

- Treatment Group: AO therapy after PCI/Stenting
- Control Group: PCI/Stenting alone
- Patient Population
  - AMI (symptom onset ≤ 6 hours)
  - Anterior Infarct
- Study Design
  - 2.8:1 Randomization
  - 304 patients (plus up to 20 run-ins) @ 22 centers
- Study Enrollment
  - 317 patients (222 AO, 79 Control; 13 run-ins; 3 randomized in error)

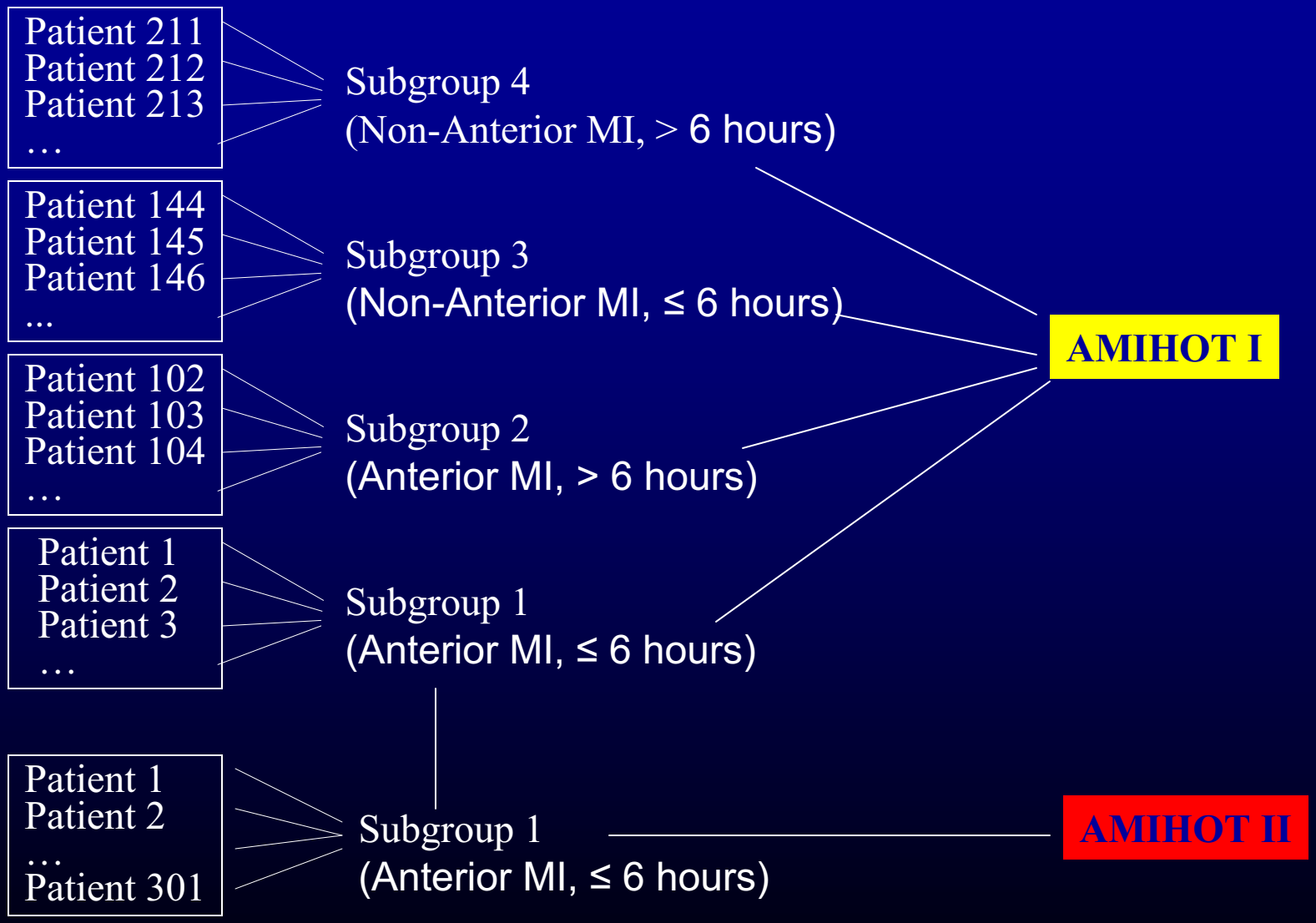
AMIHOT II Primary Endpoints

- Safety (non-inferiority)
  - Composite MACE rate - Death, Reinfarction, Revascularization and Stroke within 30 days.
- Effectiveness (superiority)
  - Infarct Size at 14 days post PCI/Stent placement

AMIHOT II
Statistical Methodology

- Hierarchical modeling was pre-specified in the protocol which allows all of AMIHOT I data to make some contribution to the statistical inference for AMIHOT II study.

Hierarchical Structure



Pre-specified model
Safety Endpoint

study i = 1,2 (1=AMIHOT I, 2=AMIHOT II) and
subgroup j (j = 1,2,3,4 for study i = 1 and j = 1 for study i = 2)

$r^{C}_{ij} \sim \text{Binomial}(n^{C}_{ij}, \pi^{C}_{ij})$

$r^{T}_{ij} \sim \text{Binomial}(n^{T}_{ij}, \pi^{T}_{ij})$

$\text{logit}(\pi^{C}_{ij}) = \lambda^{C}_{ij}$

$\lambda^{C}_{ij} = \mu_0 + \omega^{C}_{j} + \gamma^{C}_{i}$

$\pi^{T}_{ij} = \pi^{C}_{ij} + \delta_0 + \omega^{T}_{j} + \gamma^{T}_{i}$ (truncated to [0, 1])

$\omega^{C}_{j} \sim \text{Normal}(0, \varphi_{\omega}^{2})$; $\gamma^{C}_{i} \sim \text{Normal}(0, \varphi_{\gamma}^{2})$

$\omega^{T}_{j} \sim \text{Normal}(0, \tau_{\omega}^{2})$; $\gamma^{T}_{i} \sim \text{Normal}(0, \tau_{\gamma}^{2})$

Pre-specified model Effectiveness Endpoint (M1)

The mean values for study $i = 1,2$ (1=AMIHOT, 2=proposed study) and subgroup j ($j = 1,2,3,4$ in study $i = 1$ and $j = 1$ only for study $i = 2$) are parameterized as:

μ^{C}_{ij} = Mean Control group = $\mu_0 + \omega^{C}_{j} + \gamma^{C}_{i}$

μ^{T}_{ij} = Mean AO Therapy group = $\mu^{C}_{ij} + \delta_0 + \omega^{T}_{j} + \gamma^{T}_{i}$,

$$\log(y^{C}_{ijk} + 10) \sim \text{Normal}\ (\mu^{C}_{ij}\ ,\ \sigma_C^{\,2})$$

$$\log(y^{T}_{ijk} + 10) \sim \text{Normal}\ (\mu^{T}_{ij}\ ,\ \sigma_T^{\,2})$$

$$\mu^{C}_{ij} = \mu_0 + \omega^{C}_{j} + \gamma^{C}_{i}$$

$$\mu^{T}_{ij} = \mu^{C}_{ij} + \delta_0 + \omega^{T}_{j} + \gamma^{T}_{i},$$

$$\omega^{C}_{j} \sim \text{Normal}(0,\ \varphi_\omega^{\,2});\ \gamma^{C}_{i} \sim \text{Normal}(0,\ \varphi_\gamma^{\,2})$$

$$\omega^{T}_{j} \sim \text{Normal}(0,\ \tau_\omega^{\,2});\ \gamma^{T}_{i} \sim \text{Normal}(0,\ \tau_\gamma^{\,2})$$

AMIHOT II Success Criterion

- Safety endpoint: If posterior probability that treatment MACE rate π_t is no worse than the control MACE rate π_c by 6% is greater than 95%.

$$P(\pi_t < \pi_c + 6\% \mid data) > 95\%$$

- Effectiveness endpoint: If posterior probability that treatment mean infarct size μ_t is less than the control mean infarct size μ_c is greater than 95%.

$$P(\mu_t < \mu_c \mid data) > 95\%$$

AMIHOT II
Safety Endpoint

- The posterior probability of non-inferiority for the safety endpoint = 99.5%.

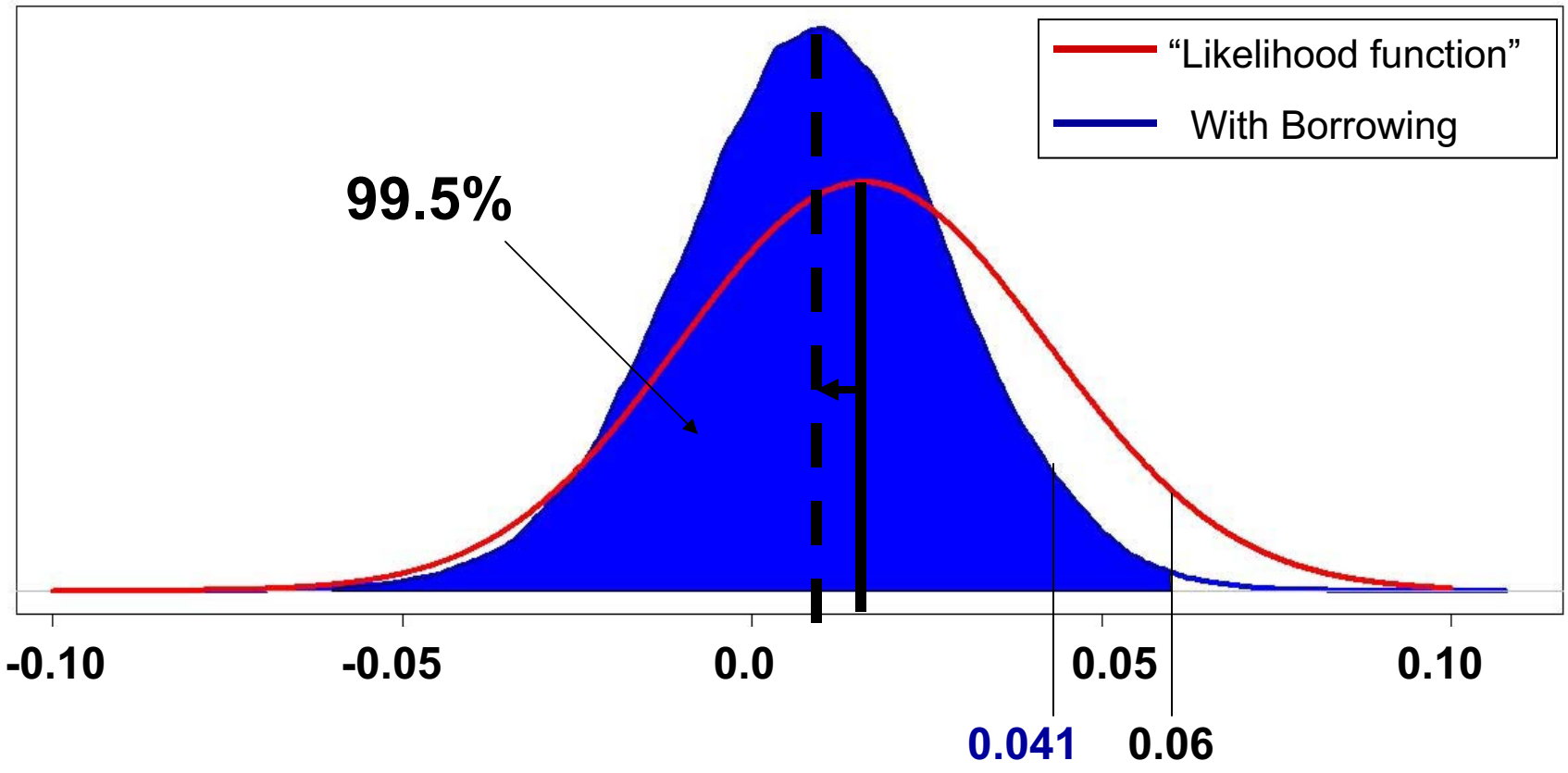
	Events				Composite MACE
Group	**Death**	**Reinfarction**	**TVR**	**Stroke**	**# Patients (%)**
Control (n = 79)	0	2	3	0	**3 (3.8%)**
AO Therapy (n = 222)	4	6	9	0	**12 (5.4%)**

AMIHOT II
Effectiveness Endpoint

- The posterior probability of superiority for the effectiveness endpoint = 95.1%.

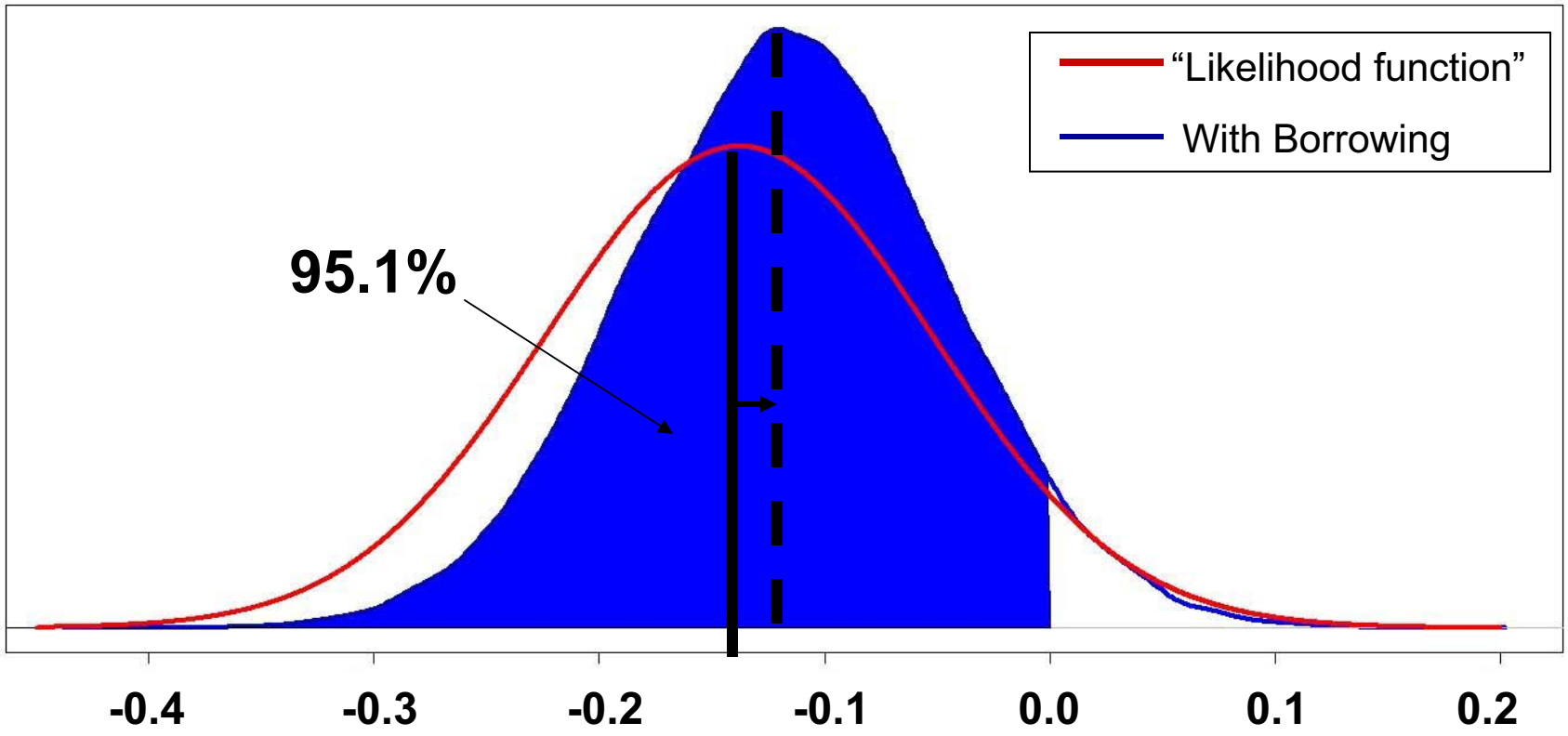
Infarct Size (%LV as measured by Tc-99m SPECT)			
ITT Analysis	**Control (n=72)**	**AO Therapy (n=209)**	**Difference (Trt – Ctrl)**
Mean ± SD	27.1 ± 19.1	23.2 ± 19.1	**-3.9**
Median	26.5	20.0	**-6.5**

Posterior Distribution for Difference in MACE rate

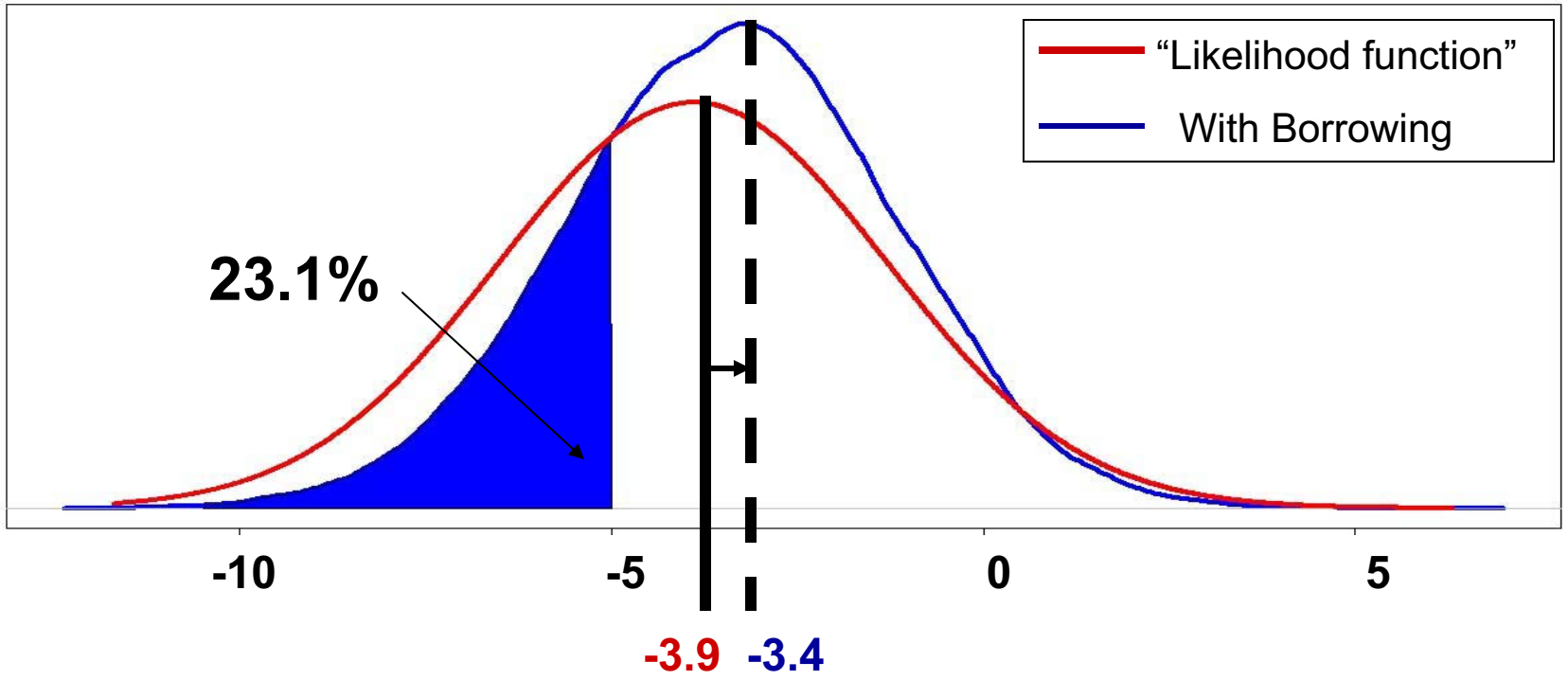


$\pi_t - \pi_c$

Posterior Distribution for Difference in Mean Log-transformed Infarct Size



Posterior Distribution for Difference in Mean Infarct Size



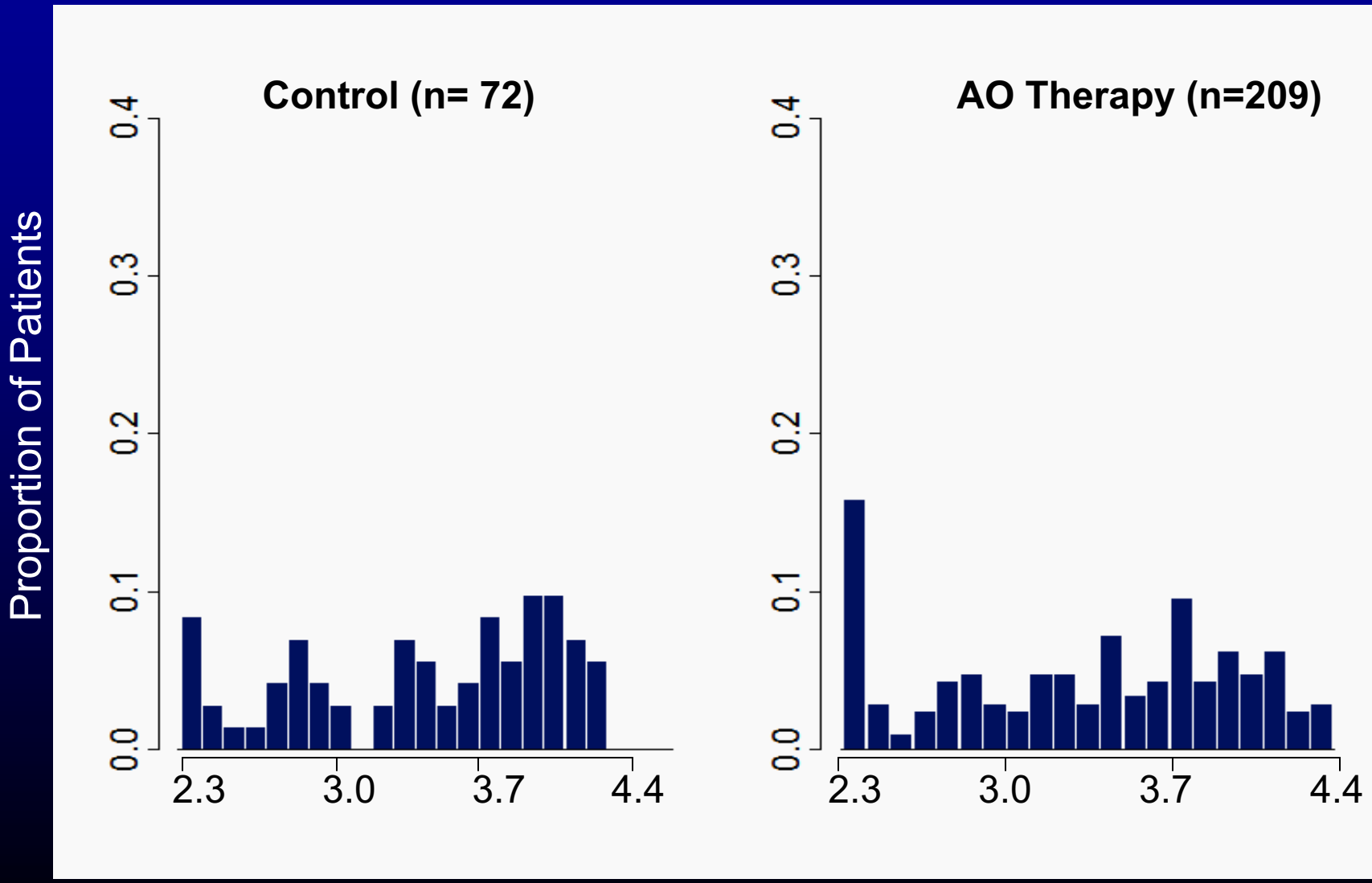
$\mu_t - \mu_c$

95% Credible Interval for $(\mu_t - \mu_c)$ = (-7.6, 1.0)

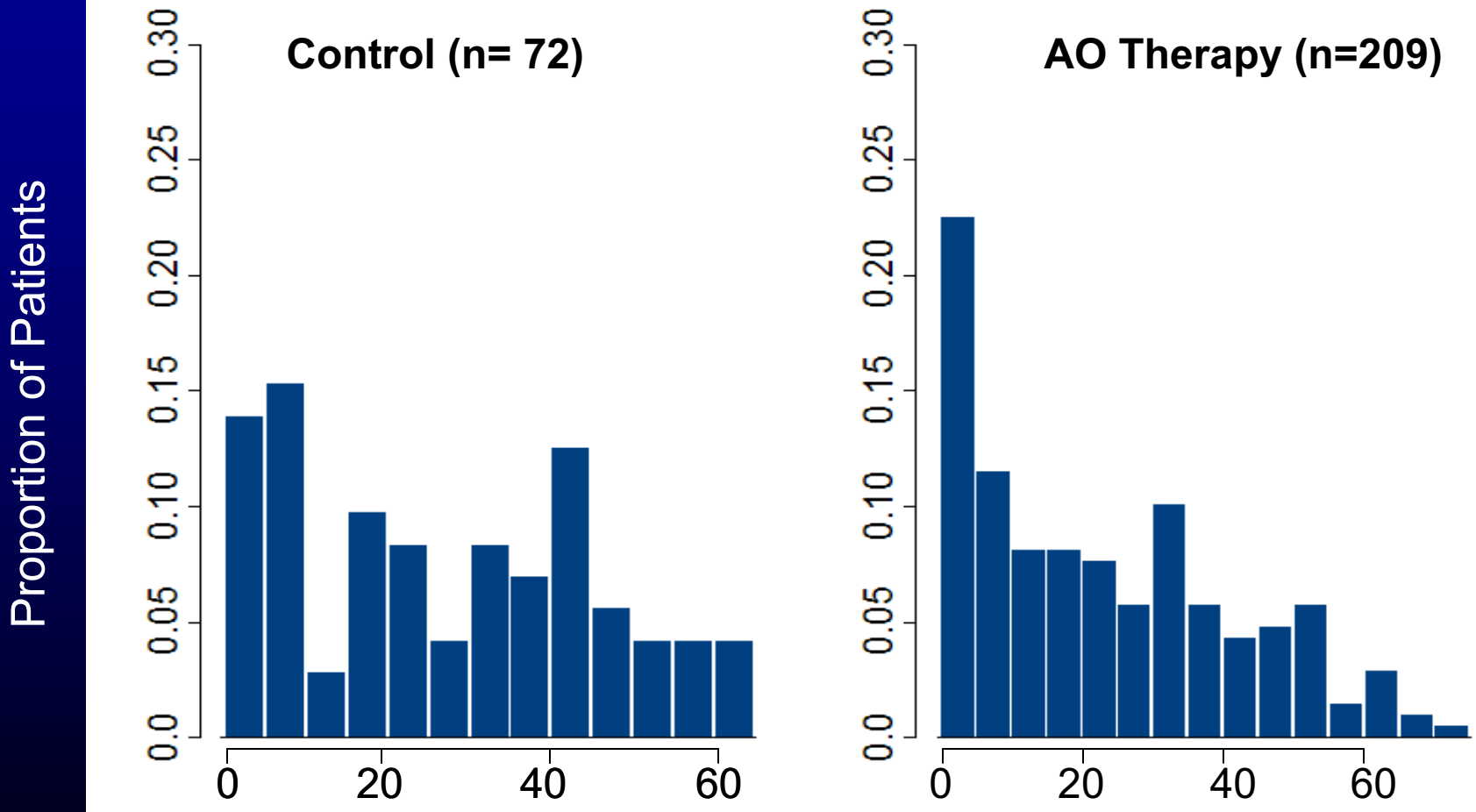
Issues related to Primary Effectiveness Endpoint

- Distributional Assumption
- Alternative Hierarchical model Structure

Distribution
Log Transformed Infarct Size



Distribution of Infarct Size



AMIHOT II
Additional Bayesian Analysis

1. Removal of normality assumption
2. Alternative hierarchical structure in which to utilize AMIHOT I data
3. Adding time to reperfusion and infarct location effects to the model
4. Adding center effect to the model

AMIHOT II – Effectiveness Endpoint

- Infarct size was categorized:
  0%, 1-7%, 8-21%, 22-39%, >39%.
- Ordinal Logistic Regression Model
- Bayesian posterior probability of superiority = 99.0%

	Posterior Probability of Superiority
Informative Prior (Borrowing)	
Model OL	99.0%
Non-Informative Prior (Non-Borrowing)	
Model OL	95.4%

Additional Bayesian Analysis

	Posterior Probability of Superiority
Informative Prior (Borrowing)	
Pre-specified Model (M1)	95.1%
New Hierarchical Model (H1)	97.7%
Two-way ANOVA Mean Structure Model (H2)	97.3%
Random Site effect (H3)	96.6%
Non-Informative Prior (Non-Borrowing)	
Pre-specified Model (M1)	94.0%
New Hierarchical Model (H1)	94.5%
Two-way ANOVA Mean Structure Model (H2)	94.5%
Random Site effect (H3)	89.3%

Statistical Summary

The primary safety and effectiveness endpoints met their pre-specified success criteria from a statistical point of view.

Following FDA Presenters

- **Julie Swain, MD** – Clinical presentation
- Shaokui Wei, MD

TherOx® Downstream® Aqueous Oxygen (AO) System

Clinical Review

Julie Swain, M.D.
Cardiac Surgeon
Consultant to FDA

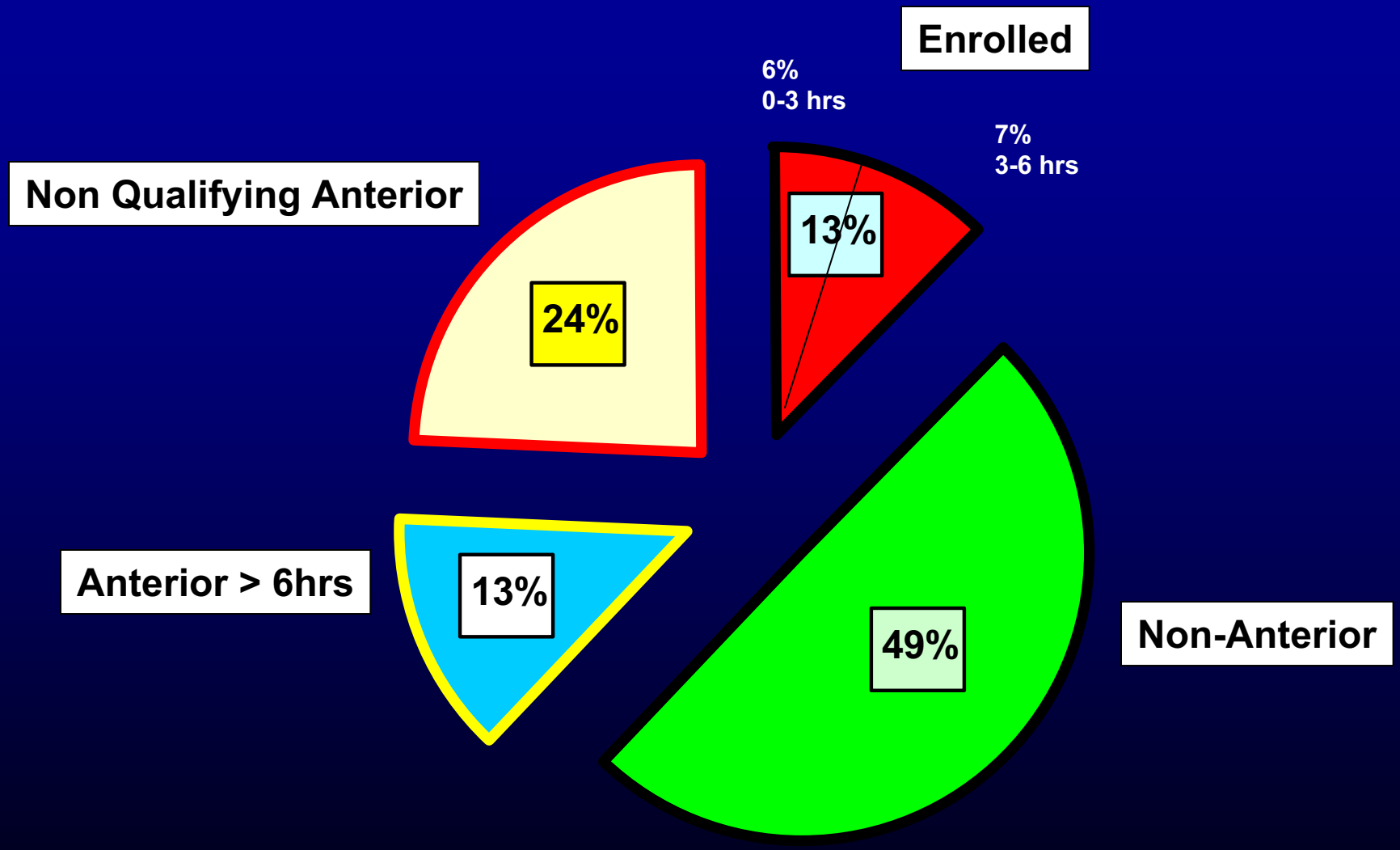
Two Trials (Bayesian analysis using both)

- AMIHOT I – **randomized 1:1**
  - **AMI (symptom onset < 24 hours)**
  - **Anterior or Non-anterior Infarct**
  - **Successful angioplasty**
  - **3 co-primary EP**
- AMIHOT II – **randomized 2.8:1, Bayesian**
  - **AMI (symptom onset <6 hours)**
  - **Anterior Infarct**
  - **Successful angioplasty**
  - **EP: Infarct size**

AMIHOT II Inclusion Criteria

- PCI indicated (probable stent)
- <TIMI 3 flow
- No shock, IABP
- No multivessel disease, no left main
- Successful PCI (stenosis <50%)
- No proximal stenosis >40% in target

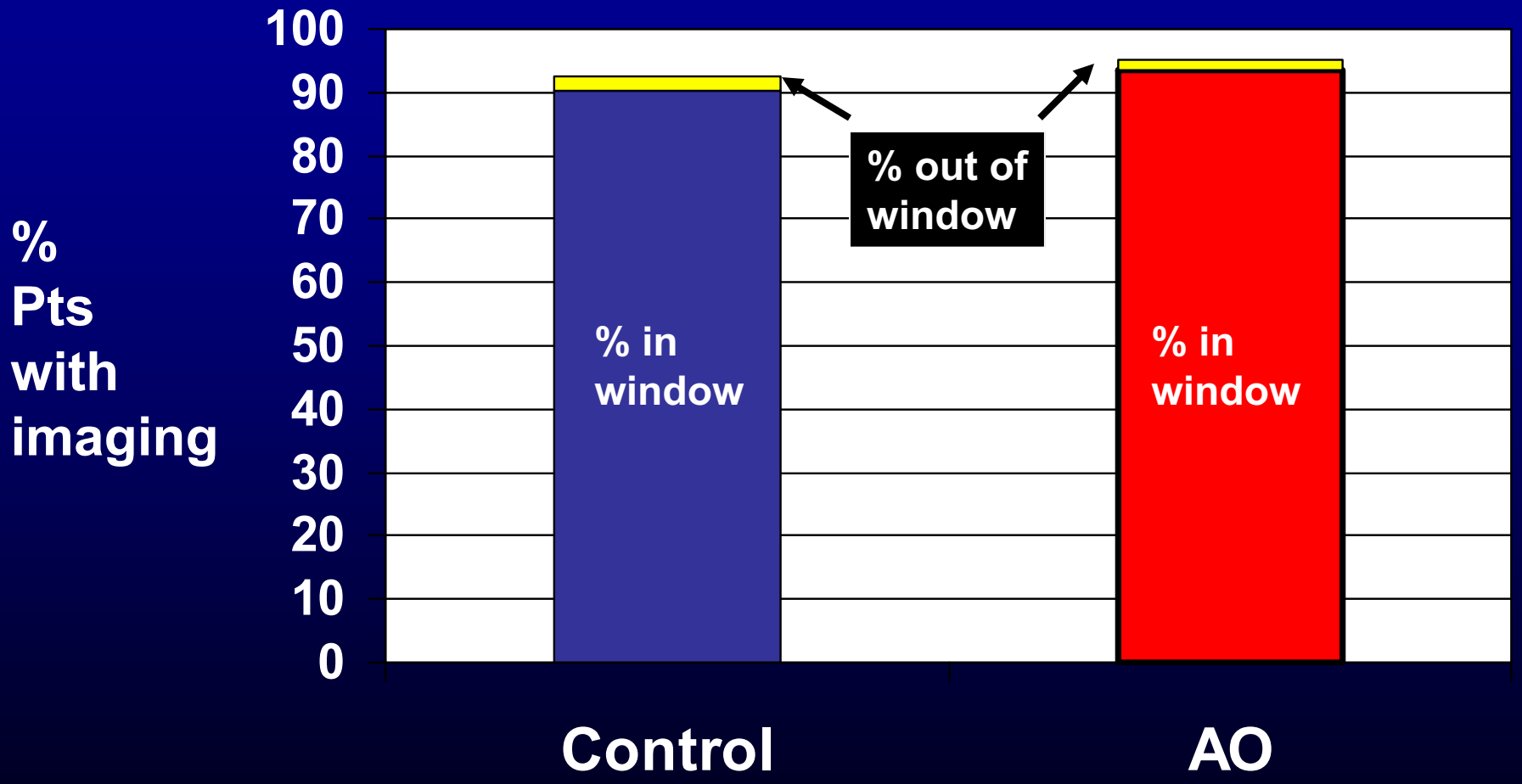
AMIHOT II Screening Log



AMIHOT II Enrollment

- 94% Caucasian, 80% Males
- 59% non-US patients
- 16% diabetics
- 47% hypertension
- 38% smokers
- Symptom onset to reperfusion = 195 min

SPECT Imaging Accountability



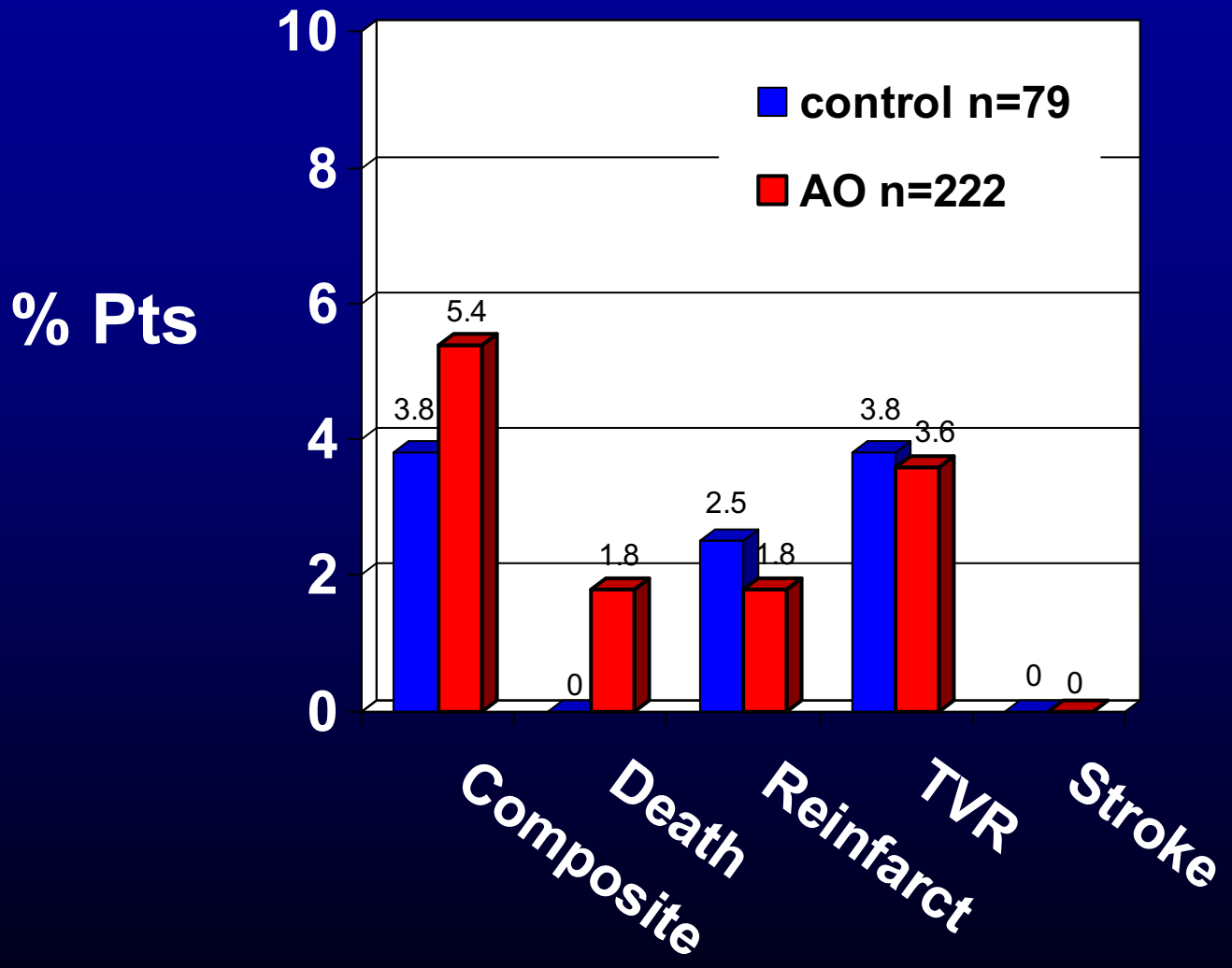
SAFETY

Primary Composite Safety Endpoint: MACE

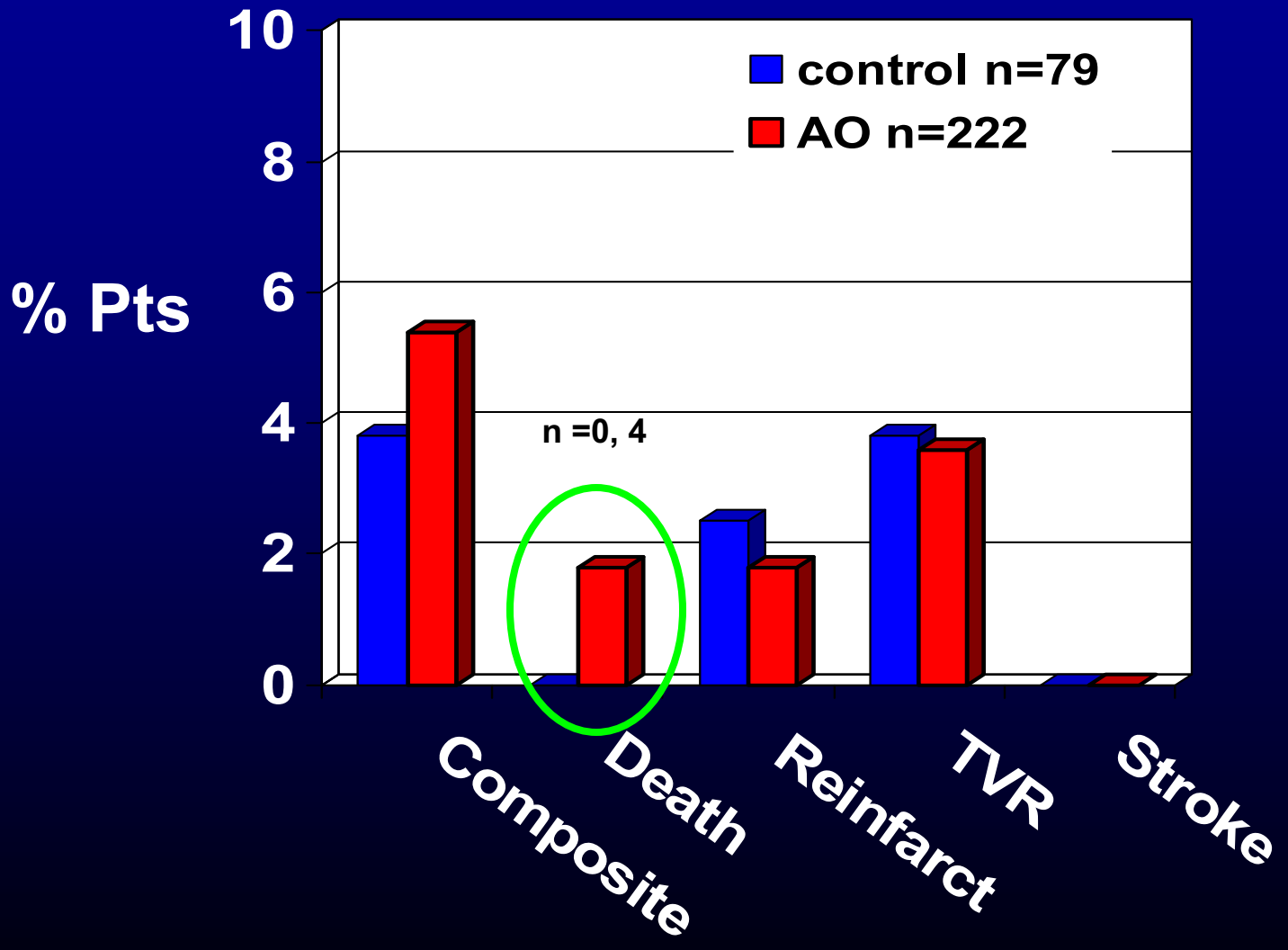
- Death
- Reinfarction
- Target Vessel Revascularization
  - *"any intervention performed in the cath lab at the time of treatment will not be considered a TVR"*
- Stroke

Non-hierarchial, components not weighted

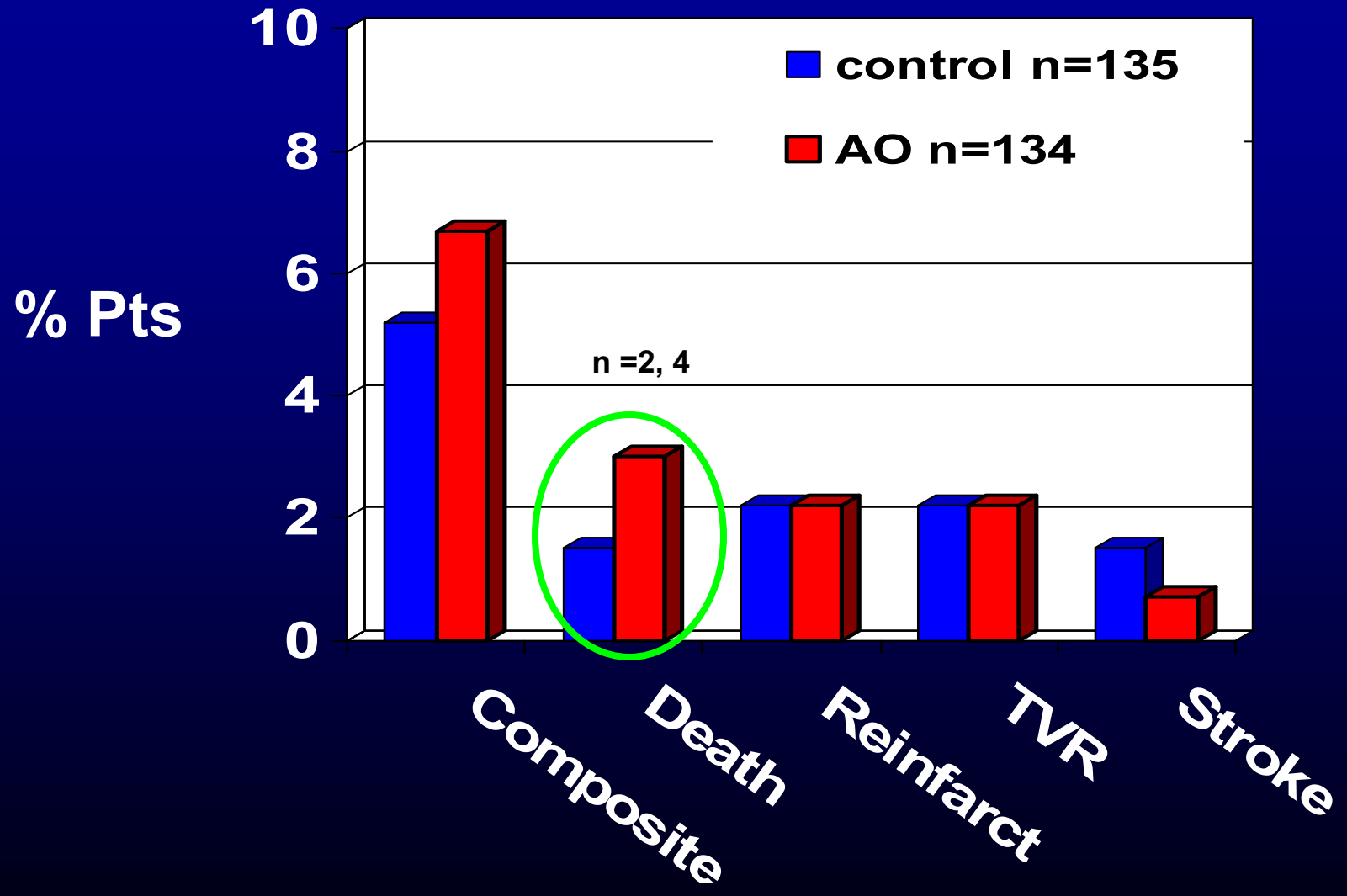
AMIHOT II MACE
(2.8:1 Randomization)



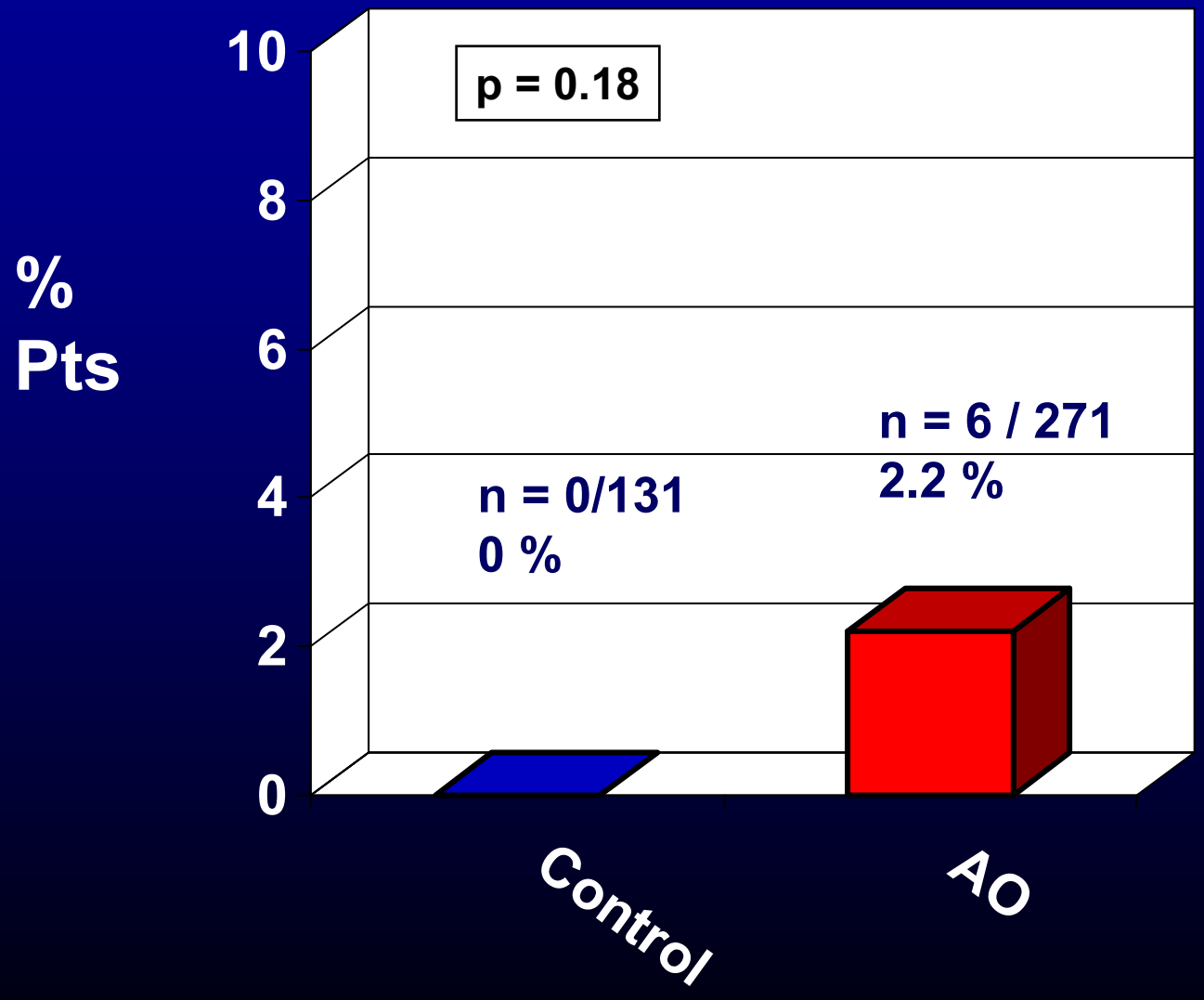
AMIHOT II MACE
(2.8:1 randomization)



AMIHOT I MACE
(All Subgroups, 1:1 Randomization)



AMIHOT I subgroup + AMIHOT II Deaths



AMIHOT I Deaths (All Patients)
(AO = 4, CON = 2) (1:1 randomization)

Control:

- **Day 0: Cardiogenic shock**
- **Day 5: Sepsis and cardiogenic shock**

AO:

- **Day 0: Retroperitoneal hemorrhage. AO catheter was on same side as PCI. Adjudicated "PCI related"**
- **Day 26: Cardiogenic shock (no additional information)**
- Day 2**: Massive anterior MI, death (AO therapy to LAD)
- Day 9**: Re-occlusion of non-target vessel stent, death

** anterior, <6 hrs subgroup

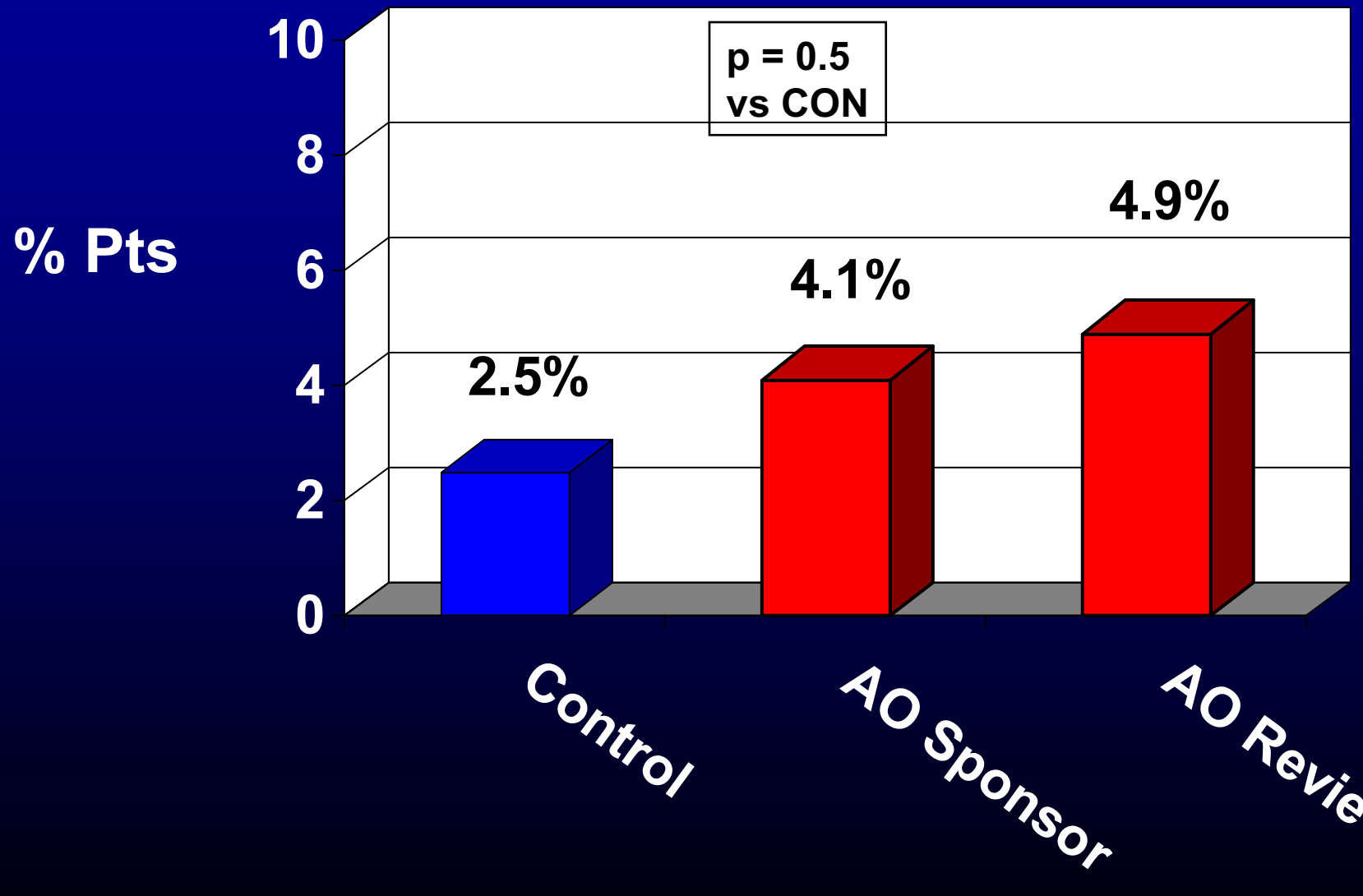
AMIHOT II Deaths
(AO=4, CON=0) (2.8:1 randomization)

Control: none

AO:

- **Day 0: V tach/fib, cardiac arrest after 4 minutes of AO therapy; LAD and Cx occlusions. Adj: "related to AO therapy".**
- **Day 4: Myocardial rupture in LAD region**
- **Day 9: Ventricular septal wall rupture**
- **Cardiac arrest, hypoxia pre-procedure (protocol deviation).**

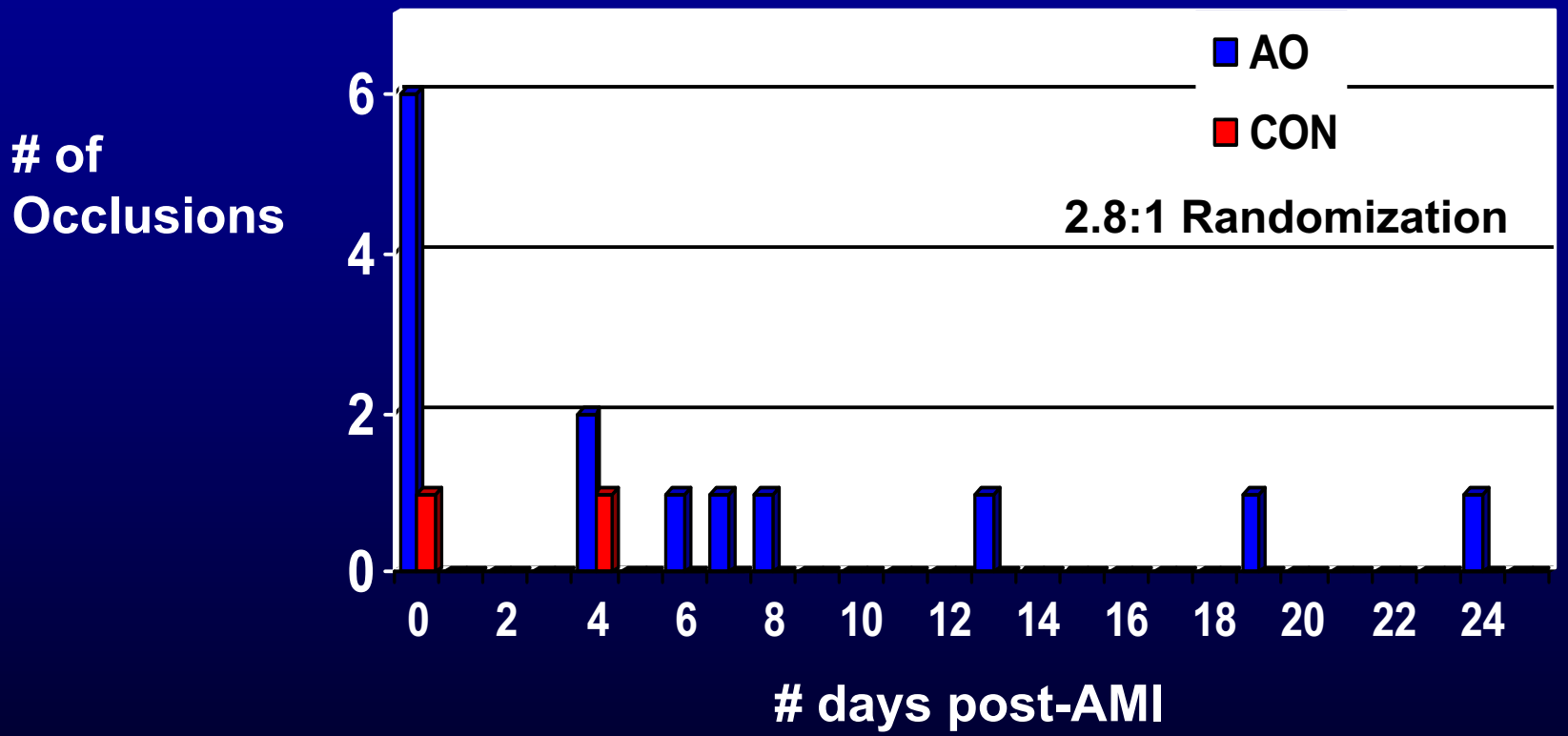
AMIHOT II
Stent Occlusions



Additional Stent Occlusions Noted by FDA

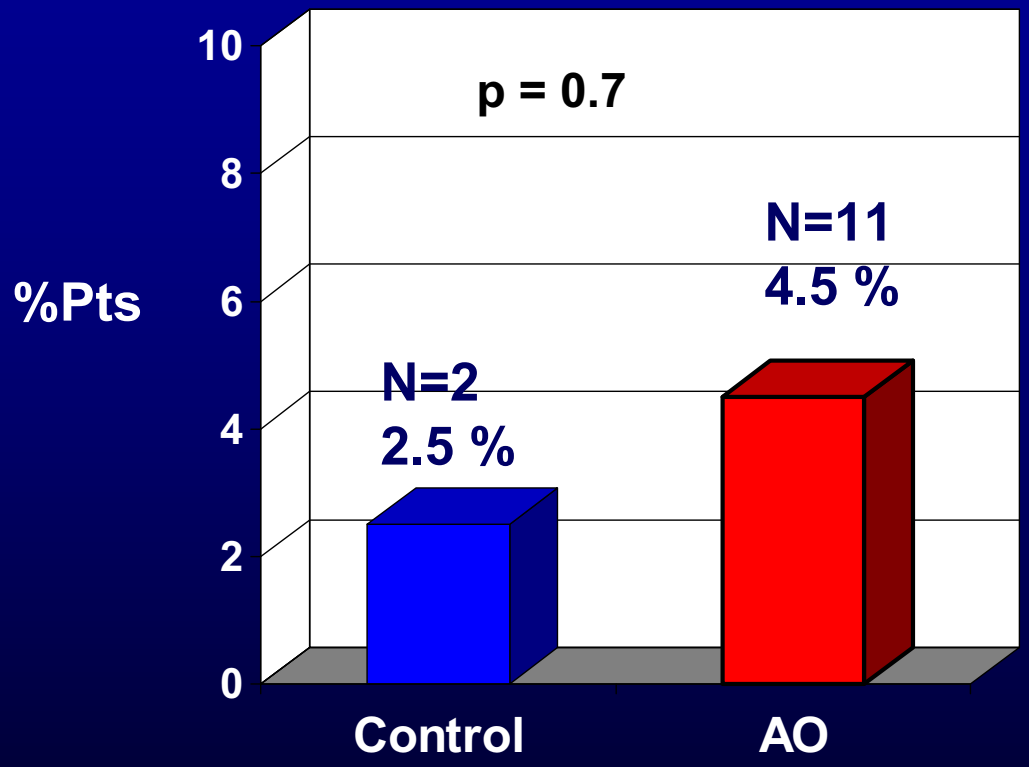
- Stent occlusion in the target artery - cardiac arrest after 4 minutes of AO therapy
- Found “incidentally” after cardiac catheterization for symptoms due to disease in another artery (Day 24)
- AO 11/222 = 4.9% vs CON 2/79 = 2.5%

Time of Stent Occlusion (AMIHOT II)



AO = 14 occlusions in 11 patients (FDA analysis)
CON = 2 occlusions in 2 patients

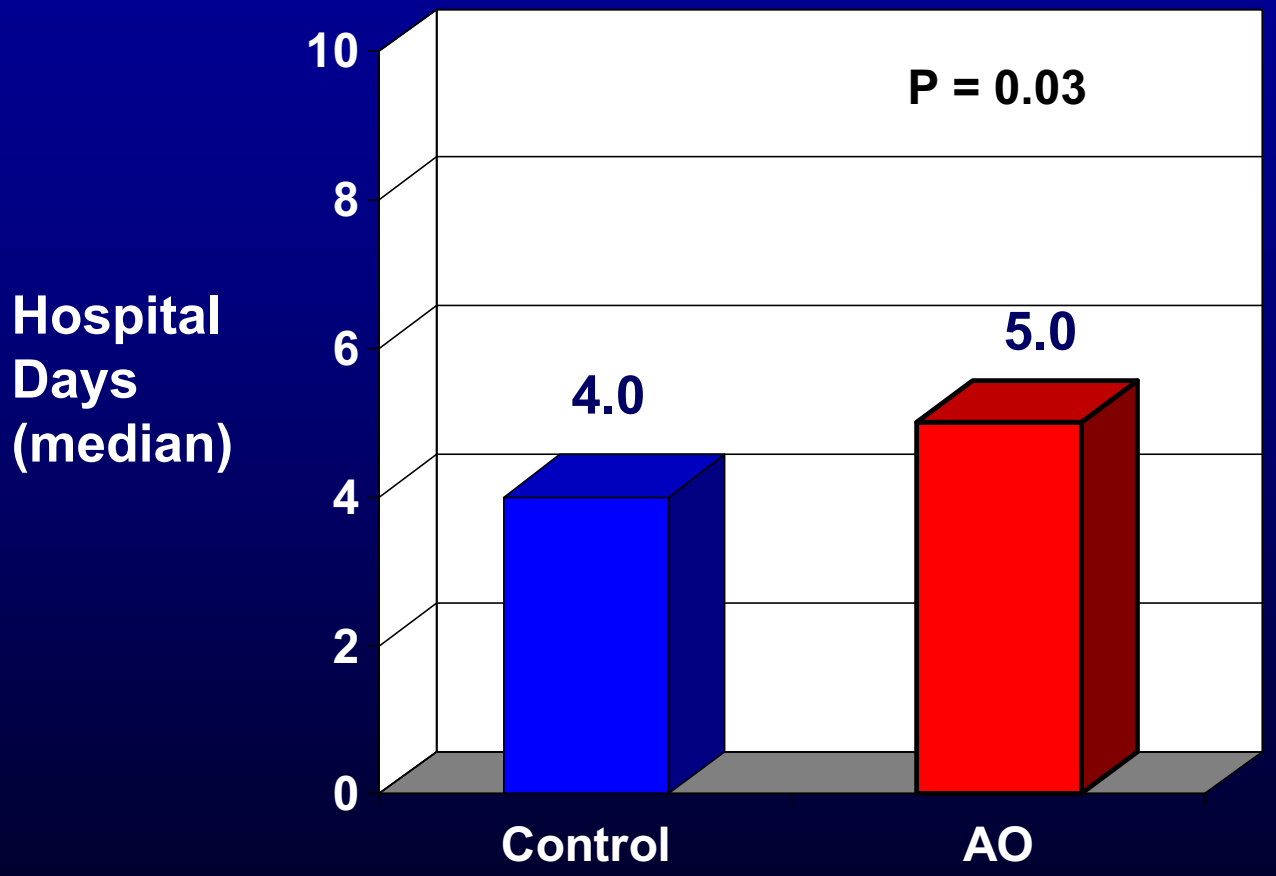
AMIHOT II Bleeding Complications (not included in MACE)



- Retroperitoneal Hematoma
- Pseudoaneurysm
- Cath Site Hematoma
- AV fistula

- 10/11 with use of TRACKER 38 catheter
- 6 AO patients required transfusions, no Controls

AMIHOT II Hospital Days

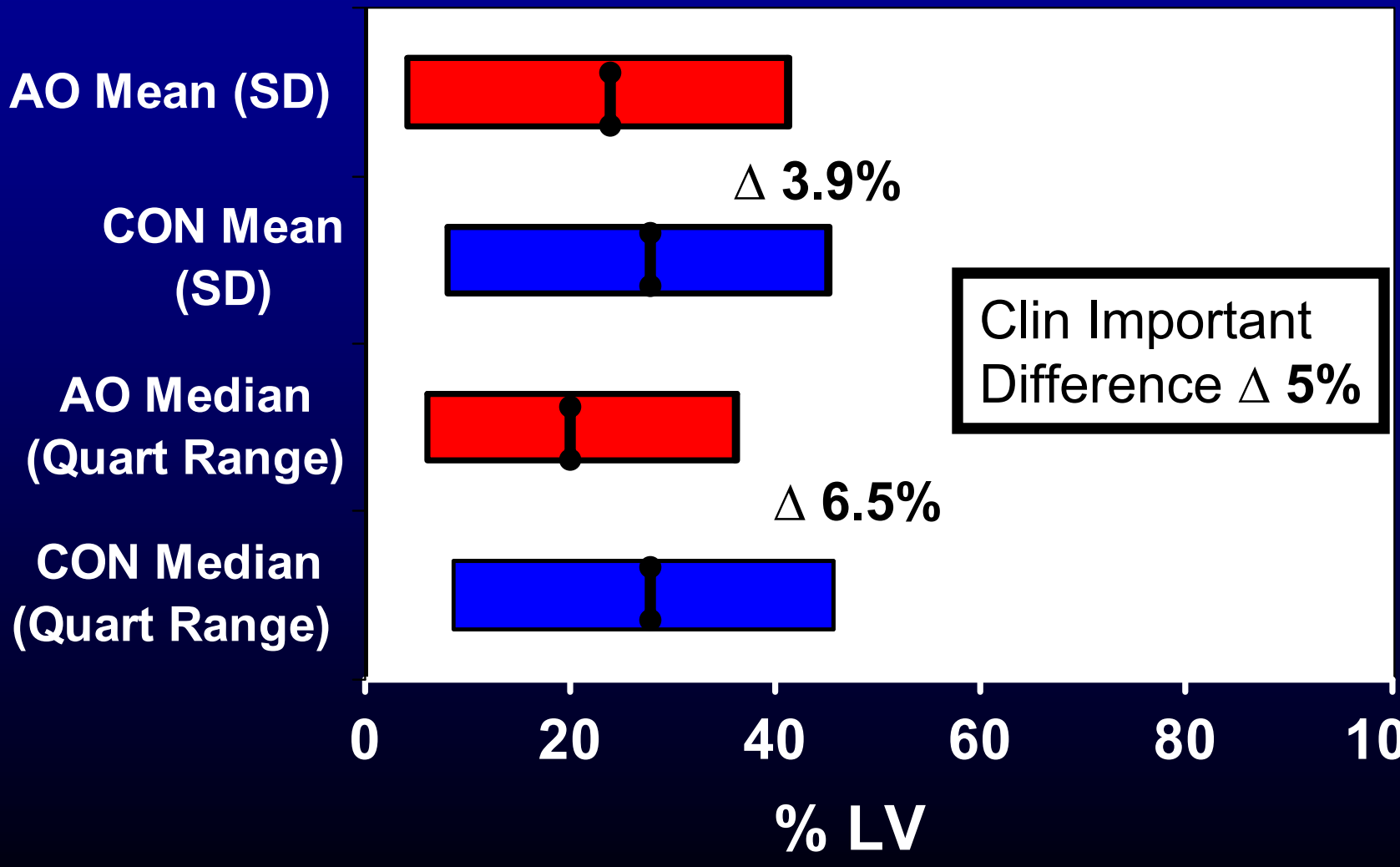


Mobile Operation of System (Intracoronary Infusion Out of Cath Lab)

- Theoretical risk (numbers too small):
  - catheter movement leading to stent occlusion
  - access site bleeding
- 27% of total patients
  - <1% of US patients
  - infusion in cath lab holding, CCU, other ICU
- Performed at only 3/22 centers
  - 48/48 (Netherlands)
  - 5/39 (Italy)
  - 1/2 (Texas)

EFFECTIVENESS

AMIHOT II Infarct Size

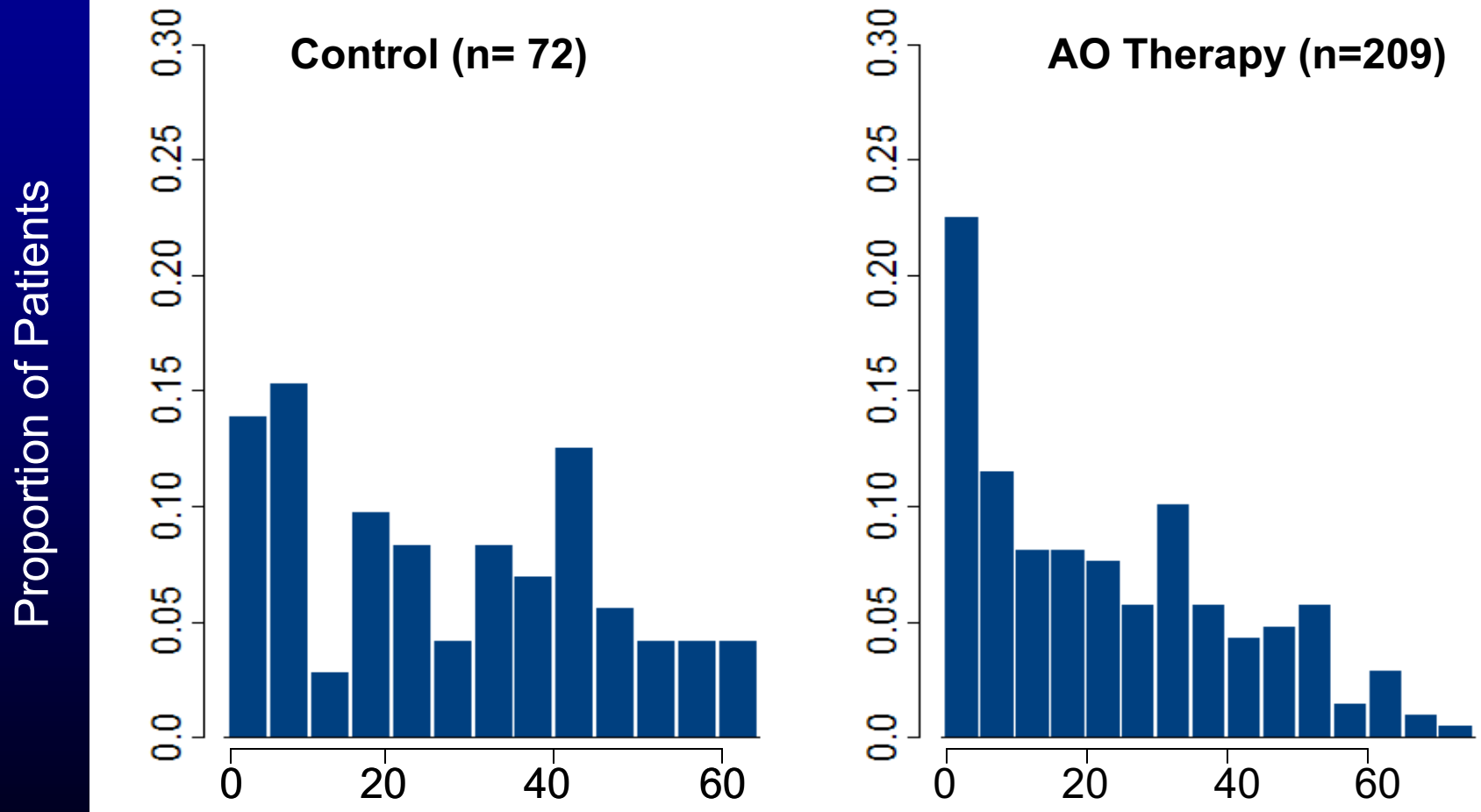


What is the Minimally Clinically Important Difference in Infarct Size: Mean vs Median?

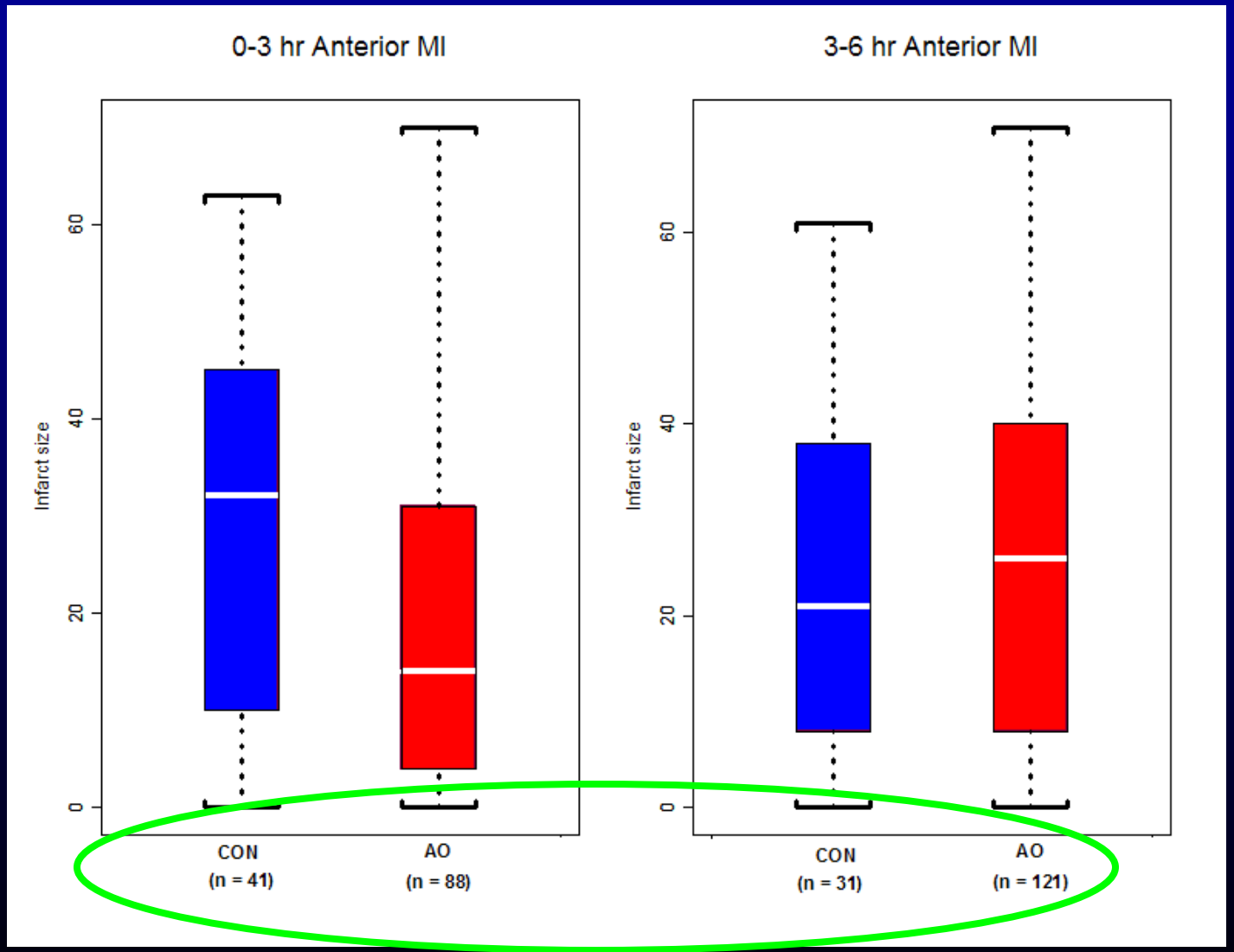
Author	Mean or Median?
Schomig	**Median**
Kastrati	**Median**
Medrano	**Mean**
Maes	**Mean**
Dakik	**Mean**
Udelson	**Mean**
Burns	**Mean**
Miller	**Median**
Chareonthaitawee	**Median**
Schomig	**Median**
Kastrati	**Median**

- Literature divided
- AMIHOT I results used mean
- AMIHOT II hypothesis was mean
- AMIHOT II Stat plan:
  "means…as well as medians"

Distribution of Infarct Size



AMIHOT II
Infarct size by Time to Reperfusion



AMIHOT II Secondary Endpoint ST Segment Recovery

- AMIHOT I: **Co-primary endpoint**
  - **ST segment recovery as evidenced by 50% lower ST-deviation vs. time trend curve area in the AO treatment group during the first three hours.**
  - **P = 0.01 favoring AO in subgroup**
- AMIHOT II : **Secondary effectiveness endpoint**
  - **no observed difference in the median accumulated ST area between the AO therapy group and Control group, at any time point (0-3 hrs, 0-4 hrs, 0-6 hrs, 0-24 hrs)**

Clinical Summary

- Modest Reduction of infarct size in the AO therapy group
- Numerically higher rates of death, stent occlusion, bleeding, and need for transfusion in the AO therapy group

Next FDA Presenter

- Shaokui Wei, MD – Post-Approval Study

Post-Approval Considerations TherOx® Downstream AO System

Shaokui Wei, MD, MPH
Division of Epidemiology
Office of Surveillance and Biometrics
Food and Drug Administration

March 18, 2009

Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

Outline

- General Principles and Objectives for Post-Approval Studies
- Overview and Assessment of Sponsor's Post-Approval Study Proposal
- Post-Approval Study Issues for Panel Discussion

General Principles for Post-Approval Studies

- To evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable device safety and effectiveness.
- Post-approval studies ***should not*** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of reasonable assurance of device safety and effectiveness.

Objectives for Post-Approval Studies

- Gather postmarket information
  - Longer-term performance
  - Community performance
  - Effectiveness of training programs
  - Sub-group performance
  - Rare adverse events and real world experience
- Account for panel recommendations

Overview of Sponsor's PAS

Study Design	A prospective, open label, single-arm study compared to subset of patients from the HORIZONS trial (Bivalirudin)
Study Endpoint	Primary: The composite incidence of MACE (death, MI and TVR at 1 year) Secondary: All causes death assessed at 1 year
Population	AMI with PCI/stenting within 6 hours of symptoms onset
Sample size	404 patients, 20-40 sites across the US
Follow-up	30, 180 days and 1 year (by telephone contact or office visit)

HORIZONS AMI Trial

- A randomized clinical trial to investigate if Bivalirudin reduces bleeding and adverse clinical events in STEMI patients undergoing primary angioplasty.
- 3600 patients, 123 centers in 11 countries. All patients had STEMI with a symptom onset < 12 hours
- Proposed control group for the PAS:
  - Subgroup of patients with anterior AMI with symptom onset to reperfusion < 6 hours
  - Baseline TIMI flow grade 0, 1, or 2, post-PCI TIMI flow grade 2 or 3

Overview of Sponsor's PAS

Hypothesis

- A non-inferiority hypothesis test will be conducted:

  Null Hypothesis: $\Pi_1 - \Pi_0 \geq \Delta$

  Alternative Hypothesis: $\Pi_1 - \Pi_0 < \Delta$

- Π_1: the incidence of MACE at 1-year in the Post-approval study
- Π_0: the incidence of MACE at 1-year in the HORIZONS trial (10.72%)
- Δ: the largest acceptable difference in incidence of MACE between the studies (6.0%)

Assessment of PAS Proposal

Study Design: Comparison Group

- A subgroup of patients from the HORIZONS trial will be used as a historical control group. This subgroup will be selected using a similar selection criteria as for the TherOx subjects in the PAS.

- Even though the inclusion/exclusion criteria looks similar between subgroup of HORIZONS subjects and the TherOx population in the PAS, the appropriateness of the HORIZONS subjects as a comparator is not well understood.

Assessment of PAS Proposal

Study Design: Endpoint

- The primary endpoint is the 1-year incidence of MACE, including death, MI and TVR.
- Should stent occlusion and bleeding be included in the primary endpoint?
- Should the events be followed out to 1 year or should the MACE rate comparison also be performed at an earlier time period, e.g., 30 days?

Assessment of PAS Proposal

Non-Inferiority Margin

- The sponsor chooses 6.0% as the non-inferiority margin and uses the 1-year MACE incidence in the HORIZONS trial (10.72%) as base rate to conduct the non-inferiority test.

- We question whether a 6.0% non-inferiority margin is clinically acceptable.

Assessment of PAS Proposal

Follow-up Assessments and Length of Follow-up

- The follow-up assessments will occur at 30 days, 180 days, and at 1 year, by phone contact or office visit .
- Given that the primary study endpoint of the study is safety, a telephone assessment may not be appropriate to determine the occurrence of adverse events.
- Is proposed follow-up appropriate to capture all relevant adverse events?

Assessment of PAS Proposal

Long-term Performance

- AO therapy is intended to reduce infarct size, thus preserving cardiac contractile function and ultimately reducing morbidity and mortality.
- We wonder whether long-term performance (e.g., chronic heart failure and cardiac mortality), should also be evaluated as part of the long-term postmarket performance of the device.

Issues for Panel Discussion

- Please discuss possible comparators, as well as an appropriate equivalence delta for a non-inferiority post-approval study.
- Please discuss whether stent occlusion, bleeding, and other events should be included in the primary endpoint.
- Please discuss whether the events should be followed out to 1 year and if MACE rate comparison should also be performed at an earlier time period, e.g., 30 days ?

Issues for Panel Discussion

- Please discuss whether the length of follow-up is appropriate and/or necessary to capture potential adverse events.

- Please discuss if endpoints such as heart failure, cardiac mortality or both, should also be evaluated as part of the long-term postmarket performance of the device.

Questions?

Evaluation of Safety

AMIHOT II MACE Endpoint Results

	Events				
Group	**Death**	**Reinfarction**	**TVR**	**Stroke**	**Composite MACE # Patients (%)**
Control (n = 79)	0	2	3	0	3 (3.8%)
AO Therapy (n = 222)	4	6	9	0	12 (5.4%)

One of the components of the composite safety endpoint was death within 30 days. In AMIHOT II there were four cardiovascular deaths (1.8%) observed in the AO therapy group compared to zero (0%) in the Control group within 30 days (Exact 95% CI for difference in death rates between AO therapy group and Control group = [-2.6%, 4.7%]). One of the deaths was directly related to the device/procedure and another two were caused by myocardial rupture. In AMIHOT I there were 4 deaths in the AO group and 2 in the Control group.

Q1a. Please comment on these mortality results.

Safety

The infusion catheter for the device is generally placed inside the newly-placed stent “just at the proximal edge.” There is a theoretical possibility of the infusion catheter disrupting the target artery or the catheter decreasing flow in the target artery, thus leading to stent occlusion. In AMIHOT II the stent occlusion rate was 4.9% for the AO patients versus 2.5% for Control.

Q1b. Please discuss the significance of the reported stent occlusion rates.

Safety

27% of patients had the intracoronary infusion completed in the CCU or cath lab holding area (only 1 US patient). There are theoretical risks associated with moving the patient while the infusion catheter is in place.

Q1c. Please discuss the potential effect mobilizing the system can have on adverse event rates and whether the AO System should be limited to use in the catheterization laboratory only.

Safety

Q1d. Please discuss whether the safety results demonstrate that there is a reasonable assurance that the device is safe for the preparation and delivery of SuperSaturated Oxygen Therapy to targeted ischemic regions of the patient's coronary vasculature immediately following successful revascularization by means of PCI with stenting that has been completed within 6 hours after the onset of anterior AMI symptoms.

Evaluation of Effectiveness

The literature justifying a 5% reduction in infarct size as representing a minimally clinically important difference is based on references using both mean and median infarct size. The AMIHOT II study showed a reduction in median infarct size of 6.5% and reduction in mean infarct size of 3.9%.

Q2a. Do the results of this study support a clinically meaningful treatment difference between AO and Control therapy patients?

Effectiveness

The Indications for Use and the intended patient population include patients with anterior infarcts who receive successful PCI within 6 hours of symptom onset. Stratified analyses for patients in the 0-3 hour and 3-6 hour symptom onset subgroups demonstrated a reduction in median infarct size of 18% in the 0-3 hr subgroup but an increase in median infarct size of 5% in the 3-6 hour subgroup for the AO therapy patients as compared to the Control group.

Q2b. Please comment on the relationship between infarct size and time to reperfusion with respect to the appropriate patient population to receive this therapy.

Effectiveness

The AMIHOT II study had a prespecified secondary endpoint of ST-segment recovery by time-trend curve at 0-3 hours, 0-4 hours, and 0-6 hours. There was no improvement in % ST resolution, ST time trends, or in quantitative ECG data.

Q2c. Please discuss the significance of the pre-specified secondary endpoint results.

Effectiveness

A *post hoc* analysis of the infarct size in each group appeared to how a leftward shift towards smaller infarct size in the AO group.

Q2d. Please discuss the findings of this exploratory analysis in the context of effectiveness of this device.

Q2e. Please discuss whether the effectiveness results demonstrate that there is a reasonable assurance that the device is effective for the preparation and delivery of SuperSaturated Oxygen Therapy (SSO2 Therapy) to targeted ischemic regions of the patient's coronary vasculature immediately following successful revascularization by means of PCI with stenting that has been completed within 6 hours after the onset of anterior AMI.

Device Labeling

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the product's potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects.

Q3a. Please comment on whether the Indications for Use section identifies the appropriate patient population for treatment with the device.

Q3b. Please suggest any changes to the labeling that you think are needed. For example, are there modifications to the warnings or clinical trial sections that you would recommend?

Post-Approval Study

The primary endpoint in this post-approval study is to evaluate the incidence of Major Adverse Cardiac Events (MACE), which includes death, myocardial infarction (MI), and target vessel revascularization at 1 year.

Q4a. Should the events be followed out to 1 year, or should MACE also be evaluated at an earlier time period, e.g., 30 days?

Q4b. Please discuss possible comparators, as well as an appropriate non-inferiority margin for a post-approval study.

Q4c. Please discuss whether stent occlusions and bleeding should be included in MACE, or any other suggestions for components of the safety endpoint.

Post-Approval Study

Currently, the clinical follow-up periods proposed by TherOx occur at 30 days, 180 days, and at 1 year.

Q4d. Please discuss whether this length of follow-up is appropriate and/or necessary to capture potential adverse events.

AO therapy is intended to reduce infarct size, thus preserving cardiac contractile function and ultimately reducing morbidity and mortality.

Q4e. Please discuss if long-term effectiveness (e.g., chronic heart failure and patient survival) should be evaluated for this therapy/device in a post-approval study. If so, what should be the comparator?